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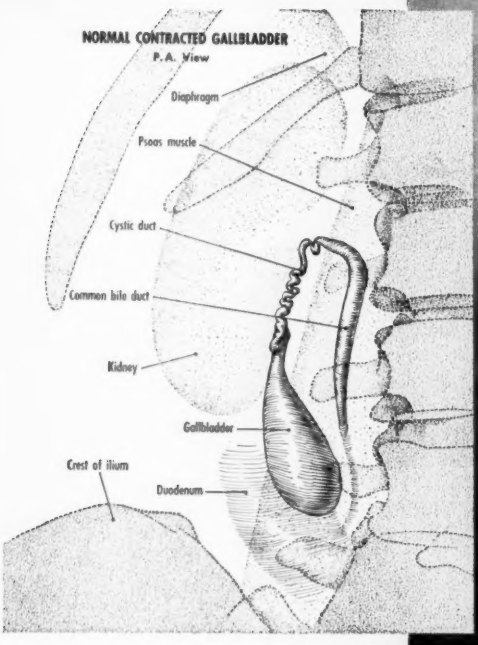

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HENRY R. VIETS* | *Boston, Massachusetts*

THE MEDICAL EDUCATION OF JAMES LLOYD IN COLONIAL AMERICA**

The speaker is not unmindful of the honor conferred upon him by the Departments of the History of Medicine and Surgery in being asked to give the third Samuel Clark Harvey Lecture. This is not a copiously elegiac age, but it is well to be reminded that Sam Harvey was a rathe and ripe mind, dedicated, as was Osler, to developing in his daily life the historical approach to medicine. As a surgeon he was bold, meticulous, and competent—serious and thoughtful at the operating table, but always seeing his patient with the humility of spirit so characteristic of greatness.

Back of all this was his long view of history, for each task was enveloped in an inquiring mind, organizing and consolidating the thoughts of his forerunners as an integral part of the problem. Whether considering a specific surgical procedure or probing into the intricate aspects of medical education, Harvey enlightened each day with an artful balance of humor and penetrating thinking. These characteristics, not the biographical details, were the products of his art, for no thought was disclosed or action motivated without the perspective of the past enlightening the present.[1]

MEDICAL EDUCATION IN COLONIAL AMERICA

Before the onset of the Revolution, in 1775, there were only two places in America where a formal course of medical education could be obtained. One was in Philadelphia, the medical school having been established there in 1765 at what is now the University of Pennsylvania. The other was in New York at King's College, where the medical department was founded in 1768. The first earned degrees in medicine were granted in 1768 to ten students by the Philadelphia school, and New York followed by giving a diploma to Robert Tucker in 1770. Both schools were small at the start and were usually attended by students from local areas. At this time most young men from New England and from the southern states were trained by the apprentice system, considered as a sound means of

* Curator, Boston Medical Library.

** The Third Samuel Clark Harvey Lecture, given at the Yale University School of Medicine on March 3, 1958.

[1] Thomson, Elizabeth H.: Samuel Clark Harvey—medical historian, 1886-1953. *J. Hist. Med.*, 1954, 9, 1-8.

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medical education by the majority of eighteenth century physicians. After an apprenticeship, boys, particularly from well-to-do families, augmented this personal instruction by study abroad, usually in London, Paris, or Edinburgh. London attracted many from New England but others went to Scotland or to the Continent. Few took a formal degree, and, indeed, before 1750 only one American is thought to have earned an M.D. abroad. This was John Moultrie of South Carolina, who won his diploma at Edinburgh in 1749. It was the custom for doctors of distinction in Europe to give private courses, most commonly in anatomy, obstetrics, and surgery. The student paid a fee, sometimes lived in the doctor's house, and at the end of the course was issued a "certificate of attendance," this being considered by most to be equivalent to a university degree. In Philadelphia the pattern was somewhat different, for young men from that progressive city went directly to the University of Edinburgh, where they entered as regular students and, if they completed their course successfully, were granted a degree. The list is a long and honorable one, beginning with Thomas Clayton (1758) and ending with Caspar Wistar (1768). In this ten-year period seven men in addition to Clayton and Wistar, studied in Edinburgh and won their degrees, including Shippen (1761), Morgan (1763), Samuel Bard (1765), Adam Kuhn (1767), and Rush (1768). Morgan and Shippen returned to found the medical department of the College of Philadelphia (now the University of Pennsylvania) in 1765, basing their school on the lines well established at the University of Edinburgh and thus establishing themselves as the leading American physicians of the time in organized medical education.

The period in general may be studied with profit by taking a single individual, such as James Lloyd of Boston, and following his development during his years of medical education up to the time of his beginning practice in 1752. In many ways his course of study was typical of the pre-Revolutionary era, and enough documents have survived to enable us to outline in some detail his life story as a young man of superior talents living in a cultured atmosphere in colonial New England. In order to afford the prescribed course of apprenticeship and subsequent European education one had to have considerable resources, both social and financial. In the case of young Lloyd these were ample. He was the scion of an English 'gentleman's' family which had prospered in America. A brief note on the family and its accomplishments will serve as a background for the narration of Lloyd's later career. That he was born in 1728 on Long Island, New York, and not in Boston, where he lived and practised medicine all his life, was due to the fact that his father was Lord of the Manor of Queens Village at the time.

THE MANOR OF QUEENS VILLAGE

Lloyd's Neck, Long Island, an attractive wooded peninsula of about three thousand acres in the eighteenth century, between Cold Spring and Huntington Harbor, was originally purchased from the Indians in 1654 and, after passing through various hands, was acquired by James Lloyd, a Boston ship-owner and merchant, partly through his wife's inheritance and partly by purchase.[2] This James Lloyd, the grandfather of Dr. Lloyd, had originally come to America from Bristol, England. He was the first Lord of the Manor of Queens Village when it was established in 1685. The Bristol family were of old Somersetshire stock, one ancestor having been a "Dr. in Physick to Queen Elizabeth."[3] It can be presumed without much question that James Lloyd, like all good Bristolians, was brought up on "Bristol milk," "the first moisture given infants in that city," according to the pious and trustworthy Fuller.[4] At all events he was an energetic Boston merchant, who, when he died in 1698, passed the manor to his children. The eldest son Henry bought out the others' interest and became the sole proprietor. He settled at the manor house, as the second Lord, in 1711 and there begat his family of ten children, seven of them being boys, with James the last child to be born (in 1728). The manor was a self-sufficient community and Henry Lloyd kept slaves, had tenants, and raised wheat, rye, and corn, vegetables and fruit, cattle, sheep, and horses. The trees on the neck were recognized as the chief source of wealth, and cord wood and timber were cut sparingly. The Lloyds were good agriculturists, actively concerned in grafting fruit trees, improving the breed of their horses and cattle, and in conserving and enriching the soil by rotation of crops and the use of fertilizers. The Lloyds were leaders in the community of Long Island and closely intermarried with distinguished Colonial families not only in New York but in Connecticut and Massachusetts. They were affiliated with the Church of England and there being no Episcopal church on Long Island, Henry Lloyd and his family used to sail from Lloyd's Neck across Long Island Sound to worship in the church in Stamford, Connecticut.

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[2] [Schmidt, Charlotte Lloyd Higbee]. *Memoranda concerning Lloyd's Neck (Manor of Queens Village), Long Island, N. Y.* Lloyd's Neck, 1884. 18 pp.

[3] Woolsey, Melancthon Lloyd: *The Lloyd manor of Queens Village.* Baltimore, 1925. 37 pp. The "Dr. in Physick to Queen Elizabeth," may have been Humphrey Lhuyd (1527-1568) as suggested in correspondence by Sir Arthur MacNalty. See: Jones, G. Penrhyn: Humphrey Lhuyd (1527-1568). A sixteenth century Welsh physician. *Proc. Royal Soc. Med.*, 1956, *49*, 521-528.

[4] Fuller, Thomas: *The histories of the Worthies of England.* New edition, with explanatory notes and copious indexes, by P. A. Nuttall. 3 vols. London, Thomas Tegg, 1840. (Vol. 3, p. 115.)

James lost his mother soon after he was born in 1728,[5] and at an early age was sent to Stratford, Connecticut, to study with the Reverend Samuel Johnson, the Anglican clergyman and Berkeleian philosopher. The clergyman's son, William Samuel Johnson, was a year older than James; they became fast friends as boys and remained so throughout their lives.[6] Lloyd lived in Stratford and in New Haven until he was seventeen, when he moved to Boston to be with his eldest brother, also named Henry, nineteen years his senior, who was the agent of purchases for the British government.[7] Since Henry Lloyd, who had married in 1737, had no children, young James became a favorite in the family, and it is through the letters that Henry Lloyd wrote to his father on Long Island that we learn about the life led by James as a youth and medical student.

THE EDUCATION OF JAMES LLOYD

The first letter from Henry Lloyd containing a reference to James, then seventeen years of age, was written to his father in Queens Village on December 31, 1745. The elder Lloyd had been concerned over the dismissal of young James as an apprentice to Silvester Gardiner, the Boston apothecary and doctor, who had apparently taken him for training. Henry wrote that Mr. Gardiner "did not treat him well, but believe he had full servants enough for his business and would not have taken him had he not been much press'd to it, but the chief thing was his wife's aversion to increasing her Family which without him consisted of 18 persons."[8] We know something of what went on through the diary of John Hartshorn, another apprentice, who was studying medicine at the time with Dr. Gardiner.[9] It is no wonder that the boy was unhappy in a household where he was treated as a servant rather than one of the family, for he came from his brother's house where there were no other children.

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[5] *Papers of the Lloyd family of the Manor of Queens Village, Lloyd's Neck, Long Island, New York. 1654-1826.* Collections of the New York Historical Society, 59-60. Two vols. New York, Printed for the Society, 1927. Hereinafter referred to as *Papers.*

[6] William was graduated from Yale in 1744. In later life he became a distinguished lawyer and the first president of Columbia College in 1787. There is no evidence that James Lloyd went to Yale College during his years of residency in New Haven in spite of his close association with young Johnson. The reason for his not doing so appears inexplicable.

[7] Lloyd, James: Dr. James Lloyd. In: Thacher, James. *American medical biography.* Two vols. in one. Boston, Richardson & Lord and Cottons & Barnard, 1828. (pp. 359-376.) The Honorable James Lloyd, Senator from Massachusetts, was Dr. James Lloyd's son.

[8] *Papers,* p. 366.

[9] Anderson, Persis G.: John Denison Hartshorn. *Bull. med. Lib. Ass.,* 1929, *n.s.18,* 19-22. The Ms. diary kept by Hartshorn from 1752 to 1756 is in the Boston Medical Library. The Anderson sketch gives only a few brief extracts.

Gardiner, who also came from a Bristol family, had been trained by Cheselden in London during his studies abroad between 1727-1735; he began his practice in Boston about the latter year. His apothecary shop at the "Sign of the Unicorn and Mortar," was the first to be established in Boston, the year before James began his brief apprenticeship. Gardiner had a thriving practice among the leading families and therefore was a natural choice as a physician to train young Lloyd. To be classed as a "servant" by the mistress of the house, however, was probably more than the lad had bargained for. Even Hartshorn barely survived a few years of the hurly-burly of that energetic household before his death while undergoing his training.

After leaving the hectic Gardiner household, James continued his training with Dr. John Clark (1698-1768), one of the leading physicians of his time and the fourth of a line of seven John Clarks, all doctors, who served the Boston community from about 1651 to 1805.[10]

Henry Lloyd wrote to his father that Dr. Clark was

> well esteem'd & besides the Towns publick business and that of the sick & wounded in the Country Service, he visitts the Governours Family & many principle familys in the Town & is the most growing Physisian we have, his demand is £400 without washing & mending (which my Aunt Steel do very reasonably) he'l have these privilidges beyond what he wou'd have had at Mr. Gardners of sitting at the same table with his master & mistress & keeping in the same Room & Company & be in every way treated as a Gentleman & be in a small family & without children. Mr. Clark says he'l be in the way of seeing as much surgery as is needfull.[11]

To study with "the most growing Physisian we have," who "visitts the Governours Family," even "without washing and mending included," and to be "treated as a Gentleman," was vastly more than Silvester Gardiner had offered. This opportunity, in spite of the high price, was quite in accord with the Lloyds' standards and one readily acceptable to Henry and his father.

Zabdiel Boylston was also considered but, wrote Henry, "his reputation no ways equal to the other Gentleman's."[12] This may seem somewhat surprising to us in view of Boylston's great reputation as the originator of smallpox inoculation in 1721 and his subsequent triumphal visit to London where he was made a Fellow of the Royal Society. But Boylston

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[10] Viets, Henry R.: *A brief history of medicine in Massachusetts.* Boston, Houghton Mifflin Company, 1930. (pp. 38-40.)

[11] *Papers,* p. 366.

[12] *Papers,* p. 366.

probably did not have a fashionable practice, visit the Governor's family, or attend the principal families in Boston, and, worthy as he appears to us, to Henry Lloyd, Boylston's reputation was not up to that of Clark's. Dr. Clark, too, was younger, only forty-seven and growing in esteem, while Boylston was sixty-six and near the age of his retirement to his father's house in Muddy River (now Brookline), where he was to raise horses and lead the life of a country gentleman. Some years prior to 1745, when James began his service with Clark, Boylston might have been the first choice, for he was an outstanding preceptor in 1736, as evinced by an "Articles of Agreement" which has come down to us of that date.[13]

Articles of Agreement between
Zabdiel Boylston and Joseph Lemmon
for the education of Joseph Lemmon, Jr., 1736.

Articles of Agreement Indented and made the eighteenth day of May Anno Domini one thousand seven hundred and thirty six Between Zabdiel Boystone of Boston in the County of Suffolk Practitioner in Physick & Surgery of the one part, and Joseph Lemmon of Charlestown in the County of Middlesex Esqr on the other part.

Whereas Joseph Lemmon Junr Son of the said Joseph Lemmon Esqr hath lived with the said Zabdiel Boylstone in order to be Instructed by him in the Arts Businesses or Mysterys of Physick and Surgery ever since the first of March last, and purposes to continue to live with the said Boylstone until the first day of March one thousand seven hundred and thirty seven if the said Boylstone shall so long live; whereupon It is agreed by and between the said Zabdiel Boylstone and Joseph Lemmon Esqr as follows vizt

Imprimis—The said Zabdiel Boylstone Doth Covenant and agree for himself to teach and Instruct the said Joseph Lemmon Junr in the Arts, Mysterys and Businesses of Physick & Surgery during the term of two years from the first day of March last, provided the said Boylstone should live so long, and if the said Joseph Lemmon Junr shall incline so long to live with and continue in the said Boystones Employ; and also to find and provide for him good sufficient and suitable Dyet and lodging during the said two years, or so long as the said Lemmon shall see cause to live with the said Boylstone

In Consideration whereof the said Joseph Lemmon for himself his Executors and admintrs doth hereby Covenant and agree to and with the said Zabdiel Boylstone to pay him two hundred pounds in full Satisfaction for his Sons Dyet and lodging and for the Instruction which the said Boylstone shall give him in the said Mysterys of Physick and Surgery during the term of two years ending in March 1737 vizt one hundred pounds thereof upon demand, and the remaining sum of one hundred pounds on or before the first day of March next, if the said Boylstone and Joseph Lemmon Junr shall be then living—

And further the said Joseph Lemmon Esqr doth hereby Covenant and agree to find and provide for his said Son Suitable and Sufficient apparel and washing during the time he shall be and remain in the Service or Employ of the said Boylstone. In witness

[13] The Ms. is in the Boston Medical Library.

whereof the s^{d} parties to these presents have hereunto interchangeably set their hands and Seals the day and year first herein beforewritten.

Signed Sealed Deliv^{d}
in the presence of us. Zab.Boylston
Edw^{d} Emerson Jun^{r}
Gillam Tailer Boston May 18th1736

Rec^{d} of Joseph Lemmon One Hundred pounds of the within Consideration
Zab. Boylston

Although we do not have the agreement between Henry Lloyd and John Clark, we may presume that it was not dissimilar to the Boylston-Lemmon contract, and that Clark, too, instructed James in the "Arts, Mysterys and Businesses of Physick and Surgery" for a term of two years, with "Dyet and lodging" included, his brother providing the "Suitable and Sufficient apparel and washing" in addition to the £400. The expenses of this education, plus the cost of support of James, seemingly gave Henry some concern. In April 1746 Lloyd paid Dr. Clark £200, apparently for the first year of James' apprenticeship. By September of 1746 Henry Lloyd had paid the last £200 to Dr. Clark. In March 1747 his brother supplied the money to young James to buy a dictionary and a pair of shoes (£10), and a pair of leather breeches (£14), all of which he duly reported to his father.[14]

EDUCATION IN EUROPE

In November 1748 James made plans to go abroad and his brother Henry wrote to his father from Boston on November 4, 1748, that

> Brother James is very desirous (& his Friends joyn with him in it) of spending a year or 18 months abroad in a Hospital when his time is out, which he may do in Paris which is cheapest & where he'l have the best opportunities for £100 Sterling a year. this alone will enable him to enter into business here immediately on his return with better advantage than he can expect without it in 7 or 10 Years. he has beha[ved] so as to be generally esteemed & will stand fair to be a Credit to his Family. if you see good to indulge his just & reasonable request (you) can by having so much warning easily provide for it.[15]

But his father could not see his way clear to finance the trip in 1747, and James had to wait until 1750 before he could go to Europe. The intervening years are not accounted for; the next note brings us to November 1750, when Henry reported that he had received two letters from James, posted in London. Arrangements were made for a letter of credit in Lon-

[14] *Papers*, p. 398.
[15] *Papers*, p. 413.

don, for Henry did not wish James to be "at any time be at a nonplus for money."[16] Incidentally, James seems to have taken with him some of his father's hair to be made into a wig in London—quite fitting for the Lord of the Manor of Queens Village in 1750.[17]

The winter of 1750-51 in London was a profitable one for James as far as his studies were concerned, but expenses ran high, and brother Henry in Boston sent £97.15.3 in March to supplement the £145 Sterling he had taken with him. He had smallpox which, besides the loss of time, as reported to his father by Henry in May 1751, "cost him £32.17.5 & £52.10/ to his instructor at Guys Hospital & £6 for anatomical Lecturs £4.10/ for Instruments £14.10/ for his Voyage & Journey makes up by far the greatest part & will not be repeated his other expences for Clothing washing & mending £13.17.4 1 Quarters Board £7.10/ being as low as can be Imagined."[18]

One of Henry's agents in London, however, wrote that, "Your Brother the Doctor is so very diligent, that we can't see him as often as we choose. I can venture to assure you he is spending both his money and time very well, and would realy advise you to contrive that he may not return till about two years hence which I'am informed will quite complete him."[19]

To "complete him," James took courses in private instruction with William Smellie and William Hunter, visited the surgeon William Cheselden, and spent a year with Joseph Warner at Guy's. Although we have no data regarding the exact dates that he began his studies and his letters during this period are not known to have survived, some evidence of his activities are hinted at in his brother's letters. The "certificates of attendance" (1752) at Smellie's and Hunter's course are intact, and Warner's appreciative letter has been published. Also a copy of the second edition of Le Dran's *Observations in surgery* (London, 1740) has survived with Lloyd's signature (1751), a book which he presumably purchased in London, and serves to fix that date. His time of departure from Boston is known approximately by a letter, written by Henry to his father on July 11, 1750: "I had not the pleasure of seeing Brother James he being met by Jones in the Bay went abroad & proceeded to Sea imediately."[20] In other words, James was abroad from the late summer of 1750 through the spring of 1752, for he was engaged in active practice in Boston by

[16] *Papers*, p. 453.
[17] *Papers*, p. 468.
[18] *Papers*, p. 478.
[19] *Papers*, p. 479.
[20] *Papers*, p. 457.

May of the latter year and at the same time his father was paying the balance of the London bills to the tune of £76.10.[21]

When James had arrived in London in 1750, his first duty after getting settled had unquestionably been to seek out and present his letters to the foremost surgeon of the time, William Cheselden.[22] After having retired in a burst of glory from St. Thomas's Hospital in 1737 at the height of his career, Cheselden took up the post of resident surgeon to the Royal Hospital, Chelsea, and there James would have visited his clinic, possibly with John Hunter, a boy of twenty, who had recently journeyed from Scotland to join his brother William. Another young man, Albrecht von Haller from Bern, was in attendance also. They are all known to have sat under the great surgeon at about this time, but unfortunately we have no definite evidence that Lloyd, John Hunter, and Haller ever met or exchanged student confidences. (Two years later we are on surer ground, for certainly James must have made the acquaintance of John Hunter when studying with William Hunter in 1752.)

Cheselden was well known in Boston, for Thomas Bulfinch, who had been apprenticed to Zabdiel Boylston, had studied with him in 1718, when Cheselden had just obtained the coveted post on the staff of St. Thomas's.[23] Sometime after 1727, when Silvester Gardiner left Boston to complete his training in Europe, he, too, worked under Cheselden and so perfected himself in urological technique that soon after his return to New England about 1735, he removed a bladder stone in the presence of the short-lived Medical Society of Boston, "according to Mr. *Cheselden's* late Improvement of the *lateral* Way."[24] But Cheselden was sixty years of age in 1750 when James Lloyd first knew him, and a semi-retired surgeon. He could hardly have had the glamor that surrounded him at St. Thomas's twenty years before when Gardiner was his pupil. Lloyd, nevertheless, must have learned the improved perineal technique for the extraction of a stone from the bladder with minimal injury to soft parts, plus a sound knowledge of anatomy upon which all Cheselden's operations were based, and something of his quickness of perception and speed of action, both essential qualities for the successful surgeon before the days of general anesthetics and antibiotics

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[21] *Papers*, p. 497.

[22] Cope, Zachary: *William Cheselden. 1688-1752.* Edinburgh, E. & S. Livingstone, 1953. (p. 97.)

[23] Packard, Francis R.: William Cheselden. Some of his contemporaries, and their American pupils. *Ann. Med. Hist.*, 1937, *n.s.9*, 533-548. Unfortunately Packard gives no references.

[24] *The Boston Weekly News-Letter*, No. 1964. November 5-13, 1741.

It was, however, from William Smellie and William Hunter that Lloyd, two years later, received his best training. Smellie in 1752 was at the height of his career as a practitioner and teacher of midwifery, for by the time James took his famous courses he had cleared away many of the superstitions which enveloped obstetrics in the mid-eighteenth century, had set forth his description of the mechanism of labor, and had become the unrivalled teacher who first established among practitioners and midwives a reasoned trust in the efficacy of the natural forces in labor under normal conditions. Smellie, in addition, gave clear indications for the application and use of forceps with precision, in accordance with the principles of the proper mechanism of labor. The ideas and ideals that he implanted into the minds of his pupils resulted in a complete revolution in obstetrical practice.[25] We may be sure that young Lloyd eagerly grasped Smellie's lectures and came to admire this talented, self-made man, who not only was a practitioner of outstanding qualifications, but also an artist, book collector, a cellist and a flautist, and a friend of Tobias Smollett, William Hunter, and Peter Camper.[26] Smellie had established himself in London in 1739 when forty-two years of age. His first pupil, who lived in his house in 1741, was a boy of twenty-three, William Hunter. Both came from the same county of Lanark, Scotland. It was natural, therefore, that Lloyd, in 1752, should also take Hunter's course in anatomy and surgery.

William Hunter had begun his anatomical lectures in 1746 and by 1752, when only thirty-four, had attained a high position as surgeon-accoucheur to the British Lying-in Hospital and had received his M.D. from Glasgow. Smellie was less cultured, perhaps even unpleasing to those of polite manners, while Hunter was urbane and conciliatory, with quick perception and delicacy of movement. The men must have been contrasting characters to young Lloyd, but he seems to have absorbed the best in each and came home bearing proudly the "Certificate of attendance" from both of his famous teachers.

In addition to his studies with Cheselden, Smellie, and William Hunter, Lloyd spent a year as a dresser with Joseph Warner at Guy's Hospital. It was from Warner that James learned the art and practice of surgery

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[25] Johnstone, R. W.: *William Smellie. The master of British midwifery.* Edinburgh and London, E. & S. Livingstone, 1952.

[26] *Petri Camperi Itinera in Angliam 1748-1785.* Edited by B. W. Th. Nuyens. Opuscula Selecta Neerlandicorum De Arte Medica xv. Amstelodami, Sumptibus Societatis, 1939. The text of Camper's travel diary is published in both Dutch and English. In 1752 Camper was making his second visit to England to study with Smellie. He did not arrive on this trip until July, so unfortunately Lloyd was deprived of the pleasure of meeting the young and talented professor from the University of Franeker as he had already left for Boston.

THESE are to certify, That during
the Course of Two Courses
Mr. James Lloyd Surgeon
hath carefully attended my LECTURES on MIDWIFERY, by which he has had the Opportunity of being fully instructed in all the different Operations and Branches of that Art. Witness my Hand this 4th Day of March 1752.

Wm Smellie M. D.

& *Teacher of Midwifery in* London.

FIG. 1. "Certificate of Attendance" granted to James Lloyd by William Smellie, March 4, 1752.

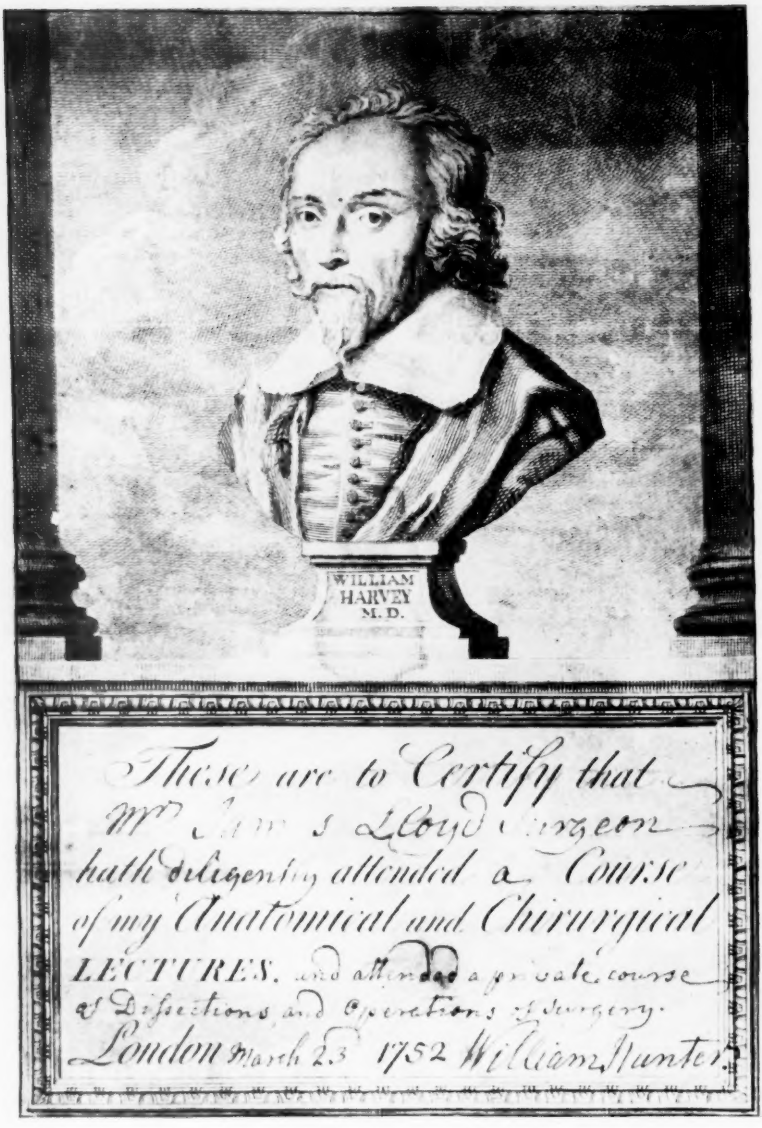
WILLIAM
HARVEY
M. D.
These are to Certify that
Mr James Lloyd Surgeon
hath diligently attended a Course
of my Anatomical and Chirurgical
LECTURES. and attended a private course
of Dissections and Operations of Surgery.
London March 23 1752 William Hunter.

FIG. 2. "Certificate of Attendance" granted to James Lloyd by William Hunter, March 23, 1752.

that only daily contact with a great surgeon in the close associations of a large hospital can supply. That Warner appreciated his "first dresser," is born out by the handwritten "certificate" he gave to Lloyd when they parted at Guy's Hospital in March 1752.

> These are to certify that Mr. James Lloyd, hath diligently attended the Hospital under me as a dresser, and the lectures of anatomy and surgery for one year; during which time, he hath behaved with the utmost diligence and care.
>
> And as I know him to be perfectly well qualified in his profession, I think it incumbent on me to recommend him in the strongest manner I am capable of; and should think myself happy, was it in my power to serve him further.[27]

THE CERTIFICATES OF ATTENDANCE

We may assume that some little ceremony accompanied the presentation of "certificates of attendance" to students by their private instructors at the end of each period of study. Two such certificates were issued to James Lloyd in 1752. These were, of course, comparable to a diploma from a recognized university as far as the young practitioner of medicine in the eighteenth century was concerned.

The first, dated March 4, 1752, was issued by "William Smellie, M.D. and teacher of midwifery in London" (Fig. 1). It certified that "during the time of two Courses Mr. James Lloyd Surgeon hath carefully attended my Lectures on Midwifery, by which he has had the Opportunity of being fully instructed in all the different Operations and Branches of that Art." Printed on light brown watermarked, laid paper, the bold signature, date, and inscription are written presumably in Smellie's hand in dark brown ink. The top half of the certificate shows an engraving of a bust of Hippocrates without the descriptive legend. The supposed portrait of Hippocrates is symbolic of medicine at its best but has no particular relationship to midwifery or surgery, the two subjects taught by Smellie. The picture must have satisfied Smellie, however, for he was still using the same form in 1757 when he issued one of his certificates to James Nankivell. This interesting copy has come down through six generations of physicians in England, almost in direct line to a present-day practitioner of the same name.[28]

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[27] In ref. 7. The original letter, quoted by James Lloyd's son, is not known to have survived. Warner's service to Guy's Hospital covers a long period, 1746 to 1780. He was still living in 1789 when Lloyd visited him on a second trip to Europe, the last survivor of Lloyd's four great teachers in London.

[28] Nankivell, P. H.: Certificate of attendance at William Smellie's Lectures, 1757. *Med. Hist.*, 1957, *1*, 279-280.

From the certificate we learn that Lloyd took two courses of lectures. Each group covered twelve sessions given in a period of two weeks. The fee for each course was two guineas and an additional guinea if a case of labor was also attended. When two courses were taken, Smellie reduced the fee from six to five guineas for the combination and also provided that the last delivery was made by the student himself. We may be reasonably sure that the energetic Lloyd took all that was offered, not only to take advantage of the reduced fee, but also to conduct a delivery under the eye of Smellie. The earlier courses were given to four students only, so the contact between the teacher and pupil must have been intimate. It is interesting that the extra guinea supplied by the students for attending a delivery was not pocketed by Smellie but was kept as a fund to aid poor patients. Thus the idea of charity to all was imbedded in the teaching of this kindly physician.

The second certificate, dated March 23, 1752, was presented to Lloyd by William Hunter, who, unlike Smellie, did not add M.D. after his name, although he had obtained a degree from Glasgow in 1750 (Fig. 2). The document is printed on the same type of light brown laid paper as the Smellie certificate, although no watermark is visible. In general the Hunter document is more elaborate and attractive, for the inscription is surrounded by a border, and the upper two-thirds contains an engraving of a bust of William Harvey, unsigned and undated, but obviously a modification of the Houbraken engraving done in 1739. The bust, now on a pedestal, is the reverse of the Houbraken engraving. The picture is particularly clear and b. lliant and closely resembled the painting by Demmel in the University of Glasgow and the copy at Saint Bartholomew's Hospital in London. This portrait was not recorded by Keynes in 1949 when he studied the Harvey portraiture.[29]

Smellie was teaching from his own residence on Wardour Street, Soho, in the Leicester Square district, when Lloyd received his certificate. It is hoped that the other three pupils, or perhaps even more, were present during the ceremony of presentation. Hunter certified that Lloyd "hath diligently attended a Course of my Anatomical and Chirurgical Lectures, and attended a private course of Dissections and Operations of Surgery." The fact that Lloyd took advantage of Hunter's private courses, as well as the more public anatomical and surgical lectures, is quite in accord with his taking a second regular course with Smellie.

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[29] Keynes, Geoffrey: *The portraiture of William Harvey.* The Thomas Vicary Lecture, 1948. London, The Royal College of Surgeons of England, Lincolns Inn Fields, 1949.

THE RETURN TO AMERICA

His precious certificates, his books, and Warner's letter now in his possession, we hope James went to church the day following the Smellie presentation, for on March 5, 1752, Isaac Maddox, the Bishop of Worcester, preached a sermon before Charles, Duke of Marlborough, the president of the "Hospital for the Small-Pox, and for Inoculation," at the parish church of St. Andrew, Holborn. The sermon was published in at least five editions, and to the fifth was added an account of the smallpox and inoculation at Boston in New England by Lloyd's fellow townsmen.[30] The Bishop made a strong plea for the Zabdiel Boylston type of inoculation; apparently Boylston's courageous experiments of 1721 were not forgotten in London in 1752.

James Lloyd returned to Boston in the spring of 1752 as well equipped to carry on the strenuous life of a physician and surgeon as any man of his time. First trained at home by John Clark, he had subsequently seen the great Cheselden in his surgery, had been taught obstetrics under the guidance of Smellie, the leading exponent of a new and practical method of delivery, had come in intimate contract with William Hunter in the dissecting room and as lecturer on anatomy and surgery, and had finally spent a year as a dresser under the eye of Joseph Warner at Guy's Hospital. With his alert mind and the driving power to make himself a master of medicine in its many aspects, the finished product was one of quality—a scholarly gentleman of superior attainments who brought to Boston in 1752 an outstanding example of medical education at its best in eighteenth century colonial America.

[30] [Maddox], Isaac: *A sermon preached before . . . Charles Duke of Marlborough, president, . . . Hospital for the Small-Pox, and for Inoculation, . . . March 5, 1752.* Fifth edition, with a new preface. London, H. Woodfall, etc. [1752].

DONALD P. BUEBENDORF
THOMAS E. CARSON
NEIL R. COOPER
MICHAEL J. MOYNIHAN
RONALD A. YANKEE*

Department of Microbiology, Yale University School of Medicine, and and the Howard Hughes Medical Institute

ASIAN INFLUENZA: A STUDY OF 150 PERSONS DURING THE 1957 PANDEMIC

In September of 1957, when this study was initiated, numerous questions had arisen concerning the epidemiological and serological characteristics of the new Type A Asian influenza virus and the vaccine developed to combat it. It was decided, therefore, to undertake a study to investigate: (i) the attack rate in a vaccinated as compared to that in an unvaccinated group living in the same community; (ii) the characteristics of the epidemic in a third group, a relatively isolated, unvaccinated population; (iii) the incidence of subclinical infections in the two unvaccinated groups; and (iv) the serological response of individuals to vaccination and to infection as determined by the hemagglutination-inhibition (HI) test and the complement-fixation (CF) test.

To study these questions three groups of about 50 subjects each were chosen and followed for a three-month period which included the entire duration of the autumn epidemic. The first study population was composed of individuals given two injections of commercially prepared, monovalent vaccine before the epidemic, the second was an unvaccinated group chosen from the same community, and the third was composed of unvaccinated, institutionalized individuals.

Paired blood samples were obtained from all participants. In the vaccinated group an initial sample was taken before the epidemic and another after the second injection of vaccine. Similarly, in the two unvaccinated groups a sample was drawn at the beginning of the study and another was taken at the end of the study from those who remained symptom-free. A sample was drawn after the acute phase of illness from all persons reporting symptoms of influenza.

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* All authors were second-year medical students during 1957-1958.

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THE STUDY POPULATIONS

A total of 150 people were included in the final analysis. The vaccinated group and one of the unvaccinated groups were comparable as to age, sex, occupation, residence, and other environmental factors. For the purposes of this study a clinical diagnosis of influenza was based upon symptoms of fever, headache, muscle and joint pains, and general malaise.

Yale Medical Center (YMC)—Vaccinated. This group consisted of 50 volunteers, 42 from the medical center and 8 undergraduate students from the college. Their ages ranged from 18 to 36 and the group included 5 females. Fifty-nine individuals were interviewed originally and bled. In the final analysis the number was reduced to 50 in the following manner: three students contracted an influenza-like illness within a week after receiving the first injection of vaccine and were excluded from the final tabulation, another was excluded because of insufficient quantity of the initial serum, another on the basis of hemolyzed serum, and the remaining four, by random selection. A second blood sample was drawn 7 to 10 days after the second injection of vaccine. From those who subsequently manifested influenza-like symptoms a third sample was drawn about two weeks following their onset. This group was self-reporting with respect to illness, although this method was supplemented by frequent personal contacts and telephone calls.

Yale Medical Center (YMC)—Unvaccinated. This group was composed of volunteers chosen from the same population as the vaccinated population. Their ages ranged from 17 to 59 and the group included 8 females. A blood sample was obtained from each person at the beginning of the study, a second approximately two weeks after the onset of symptoms, provided they became ill, and a second sample from those who remained well at the termination of the study in December. This group was also self-reporting.

Southbury—Unvaccinated. This group was chosen from patients at the Southbury Training School, an institution maintained by the State of Connecticut for the mentally retarded. Approximately 1,600 patients are segregated in cottages containing about 15 to 40 patients apiece, each cottage population representing a closely knit group with little outside contact except with persons in other cottages. None of the patients in the school was vaccinated. At the beginning of our study there, which was somewhat after the study commenced at the Medical Center (October 22 and September 25, respectively) the epidemic had begun in all of the cottages. In the three cottages which were chosen for study there were as yet very

few cases. The ages of the patients ranged from 15 to 62 and the group included no females. A total of 54 patients was studied and none of those chosen had as yet shown any symptoms of influenza. This number was subsequently reduced to 50 by random selection. Blood samples were collected initially from all 54 patients, and a second sample was taken either two to three weeks after the onset of symptoms from those who became ill, or at the close of the study from those who remained well. Due to the close supervision of the patients at Southbury, accurate records were available concerning the clinical attack rate as well as the temperatures of all those who showed symptoms.

MATERIALS AND TECHNIQUES

The vaccine. A commercially prepared monovalent, Asian strain vaccine, obtained from extra-embryonic fluids of infected chick embryos and inactivated with formalin, was used. It was said to contain 200 CCA units per ml. The vaccine was given intradermally in two 0.1 ml. injections separated by approximately two weeks.

Sera. After venipuncture all blood samples were permitted to clot at room temperature and then were centrifuged twice at 2,000 to 2,700 rpm. The sera were separated and frozen at —28° C. until the analyses. All sera were heated at 56° C. for 30 minutes. None of the sera was anticomplementary.

Previous investigators have stated that the A/Japan 305/57 strain of Asian virus, used in our analyses, was relatively insusceptible to nonspecific inhibitors,[3, 5] while others have used potassium periodate[1, 2] or cholera filtrate[5] to inactivate such inhibitors. No such substances were employed in the present study, since preliminary assays on several of the heated sera showed no evidence of nonspecific inhibition. However, two paired sera spontaneously agglutinated chicken erythrocytes in the absence of virus. These sera were treated twice at 0° C. with chicken red cells and subsequently showed no spontaneous agglutination.

Serum dilutions were prepared from 1/5 to 1/320. One ml. of heated serum was added to 4 ml. of veronal buffer, and twofold dilutions were made by serial transfer of 2.5 ml. volumes, using a clean 5 ml. pipette for each transfer.

The virus. The A/Japan/305/57 strain of influenza in fifth egg passage was used throughout.

The optimal concentration for complement-fixation tests was determined as shown in Table 1. Reaction mixtures were prepared containing 0.2 ml. of serum dilution (Asian convalescent serum), 0.5 ml. of guinea pig serum containing 5 $C'H_{50}$ units of complement, and 0.5 ml. of each dilution of virus in veronal buffer. The amount of complement fixed at each dilution of virus was measured as described below under *Complement Fixation test.* As may be seen, maximal fixation at the highest dilution of serum occurred in the mixtures containing a 1/80 dilution of virus. Therefore, 0.5 ml. of a 1/80 dilution subsequently was used in all CF analyses.

Similarly, the optimal dilution of virus for hemagglutination-inhibition was determined in mixtures containing 0.25 ml. of each serum dilution (Asian convalescent serum), 0.5 ml. of dilutions of virus in saline, and 0.3 ml. of a 0.5 per cent suspension of chicken erythrocytes. By this technique, the virus titrated 1/240 taking 2+ hemag-

glutination (50 per cent) as the endpoint. In subsequent tests, 0.5 ml. of a 1/80 dilution of virus, i.e., three 2+ doses, was used in each reaction mixture.

Complement (C'). Commercially prepared complement from Carworth Farms consisting of fresh frozen pooled guinea pig serum was used. The C′ was titrated beforehand and found to contain greater than 200 $C'H_{50}$ units per ml. It was diluted for our analyses so that 0.5 ml. contained 5 $C'H_{50}$ units.

Sheep erythrocytes for complement-fixation. The sheep red blood cells, appropriately washed and suspended in veronal buffer containing bovine serum albumin (SAVB),

TABLE 1. DETERMINATION OF OPTIMAL CONCENTRATION OF VIRUS FOR COMPLEMENT FIXATION WITH SERUM FROM A PATIENT WITH ASIAN INFLUENZA

	Dilution of serum								
Dilution of virus	*1/5*	*1/10*	*1/20*	*1/40*	*1/80*	*1/160*	*1/320*	*1/640*	*Buffer only*
1/5	0	0	0	0	tr	2	4	4	4
1/10	0	0	0	0	1	3	4	4	4
1/20	0	0	0	0	0	4	4	4	4
1/40	0	0	0	0	0	3	4	4	4
1/80	tr	0	0	0	0	0	4	4	4
1/160	4	2	1	0	0	1	4	4	4
1/320	4	4	4	3	3	4	4	4	4
1/640	4	4	4	4	4	4	4	4	4
Buffer only	4	4	4	4	4	4	4	4	4

Results of residual C′ reactivity upon addition of sensitized sheep erythrocytes are expressed as 4 for complete lysis indicating an excess of C′ remaining, 0 for no lysis indicating complete fixation of C′ during the test, and 3, 2, or 1 for intermediate degrees of lysis.

were standardized on the Beckman spectrophotometer to an optical density of 0.680. A complete description of the technique for sensitization may be found in Osler, Strauss, and Mayer.[6] In brief, the standardized erythrocytes were sensitized with an equal volume of amboceptor (serum of rabbits immunized with boiled sheep red cell stromata) calculated to give about 1,000 antibody molecules per red cell. The resulting suspension was incubated at room temperature for 30 minutes and then refrigerated until use.

The CF tests. To each of the seven CF tubes 0.2 ml. of each dilution of serum was added (serum dilutions 1/10 to 1/320 and a control without virus at the lowest dilution as a test for anti-complementary action of each serum). The tubes were cooled before the addition of 0.5 ml. of complement (5 $C'H_{50}$ units) to each tube; 0.5 ml. of virus was then added to the tubes (except the first) and they were placed in a bath at 0° C. overnight, followed by a 20-minute incubation at 37° C., to allow fixation to take place. Then, 0.3 ml. of sensitized sheep red cells was added to each tube as an indicator for residual C′ and incubated for 60 minutes at 37° C. with constant mixing. The tubes

were then centrifuged and read, the degree of lysis determined visually, taking 2+ lysis as the endpoint for expression of titer.

Chicken erythrocytes for hemagglutination-inhibition. A suspension of chicken red blood cells was prepared by washing the cells three times with isotonic saline, followed by suspending them in saline to make a 0.5 per cent suspension. No red cells older than three days were used.

The HI Tests. To each of the six HI tubes, 0.25 ml. of each serum dilution was added (serum dilutions 1/5 to 1/80 and a control without virus at the lowest dilution as a test for spontaneous hemagglutination). Then 0.5 ml. of a 1/80 dilution of virus was added to the tubes, and they were allowed to stand for 20 minutes at room temperature before the addition of 0.3 ml. of chicken erythrocytes. After 30 to 40 minutes the patterns of the settled erythrocytes were read, taking 2+ hemagglutination as the endpoint. The reciprocal of the serum dilution producing this reactivity was recorded as the titer. With sera showing no hemagglutination at the 1/5 dilution, a titer of 2.5 was assumed as the maximum for comparison with the titer of the paired serum.

Significance of the tests. A threefold increase in titer was taken as significant in both the CF and HI tests. We believe this value to be significant because of the care exercised in preparation of reagents and in performing the analyses. As may be seen in Table 1, these techniques were sensitive enough to detect a twofold difference in antibody concentration. This is apparent in that the degree of lysis was altered markedly by a twofold dilution of serum especially in mixtures containing the 1/80 dilution of virus. As would be expected because of the sigmoidal response curve in immune hemolysis, the differences were most obvious when 2+ lysis (50 per cent) was used as the endpoint.

The sera showing a fourfold rise, however, are included for purposes of comparison. The number of people showing a threefold and fourfold rise in general was of the same magnitude in both unvaccinated groups, as may be seen from Tables 2, 3, and 4. In the vaccinated group, where the titer rise in response to the vaccine was in general very low, there is a difference in the numbers of people showing a three- and fourfold rise.

RESULTS

Before an analysis of the paired sera was undertaken, it became obvious that the three groups under study differed greatly in regard to the number of influenza-like attacks reported on a solely clinical basis. As shown in Table 2, the vaccinated group at the Yale Medical Center (YMC) reported an attack rate of only three out of 50, while the Yale unvaccinated group reported 20 out of 50 and the Southbury unvaccinated group, 33 out of 50.

The distribution of clinical symptoms on a time basis showed that all three groups were affected within a relatively short period. The YMC vaccinated group had two of its three attacks during the week of October 20-26. The height of the attack in the YMC unvaccinated group came one week earlier, October 13-19, when 11 out of the 20 were ill. At Southbury, all 33 of the clinical cases were reported during the week of October 20-26. In terms of the total time involved, all clinically reported cases of influenza fell between September 25 and November 4, 1957.

For the two YMC groups, no precise information is available concerning the duration of illness or the temperatures. However, with the Southbury unvaccinated group it was possible to study both of these variables. The temperatures ranged from a low of normal to a high of 104° F. The spread was an even one between these two extremes. The duration of

TABLE 2. THE CLINICAL ATTACKS AND SEROLOGICAL RESPONSES IN EACH OF THE THREE STUDY GROUPS

	Y.M.C. Vaccinated*	*Y.M.C. Unvaccinated*	*Southbury Unvaccinated*
Influenza-like attack on clinical basis	3/50	20/50	33/50
Influenza-like attack with antibody rise by either HI or CF			
threefold rise	1/3**	16/20	28/33
fourfold rise	1/3	12/20	25/33
Antibody rise by either CF or HI without influenza-like attack			
threefold rise	26/47	9/30	11/17
fourfold rise	15/47	8/30	9/17

* In addition to this group of 50 are three who were excluded from the study. These three did not receive a second injection of vaccine because of presumed influenza attacks shortly after receiving the first injection.

** This figure represents the third serum sample taken on the three persons who reported influenza symptoms. A second sample taken after vaccination is not included here, although it showed two of the three to have had an antibody rise.

illness ranged from 1 to 11 days, with most patients reporting symptoms subsiding after about four days.

Paired sera from each patient were analyzed by both the CF and HI tests. Attention is called to the serological confirmation, i.e., a rise in titer by either CF or HI test, of the clinically reported attack rate mentioned above. In the YMC unvaccinated group, 16 of the 20 illnesses were confirmed serologically, and similarly at Southbury 28 out of the 33 were verified. Of the five Southbury patients in whom no increase in antibody was detected, three originally were regarded as questionable influenza with temperatures all below 99.4° F., a fourth had a temperature of 100° F., while the fifth recorded 102° F. The sera taken after the clinical illness

on the three YMC vaccinated patients confirmed only one of the clinical attacks as influenza. Of the remaining two patients, one was later diagnosed serologically as infectious mononucleosis, but no specific diagnosis could be established for the third.

An antibody rise as demonstrated by either CF or HI occurred in some patients not reporting any clinical illness and is shown in Table 2. This was the predominant response in the YMC vaccinated group (26 out of 47), while the YMC and Southbury unvaccinated groups showed rises in 9 of 30 and 11 of 17 respectively. The results with both serological tests are shown for all persons reporting influenza-like illnesses in Table 3. The three groups under study are divided into three categories, depending on whether they had a rise in antibody by both CF and HI, by HI only, or by CF only.

Notable is the variation between the 2 out of 20 in the YMC unvaccinated and the 16 out of 33 in the Southbury unvaccinated groups who showed threefold rises by both HI and CF tests. In the YMC unvaccinated population there is a great preponderance of increases by CF only as compared with those by HI only: 13 out of 20 as opposed to one out of 20.

There is a similar although less striking pattern in the Southbury group where 9 out of 33 had only a CF response and 3 out of 33 had only an HI increase.

Some differences in antibody response also occurred in those patients who did not report clinical attacks of influenza (Table 4). The differences were limited to the results of the CF tests in that there were 12 of 47 vaccinated persons who showed only a rise by CF, while only 3 out of the 47 unvaccinated (30 YMC and 17 Southbury) showed such a response. On the other hand, the numbers in each of the three groups showing only an HI rise (8 of the 47 vaccinated and 9 of the 47 unvaccinated) were similar. Likewise, there were 6 out of 47 vaccinated and 8 out of 47 unvaccinated showing a rise by both CF and HI. In brief, there was a total of 20 out of 47 unvaccinated and 26 out of 47 vaccinated subjects who showed a threefold or greater antibody response. In these cases, the responses may have been due to asymptomatic influenza in the unvaccinated people and to the injection of killed virus, to asymptomatic infection, to antibody to egg impurity in the vaccine, or to a combination of these possibilities in the vaccinated population.

An additional test on all YMC sera showing a CF rise but no change in HI was performed in order to exclude egg antibody as responsible. Quantitative CF tests showed the vaccine to contain 200 μg. of egg albumin per ml. Since a total of 0.2 ml. was injected into each subject, i.e., approximately 40 μg. of egg albumin, it was not inconceivable that egg

antibodies could have developed. It was further found that the viral suspension which was used for the *in vitro* CF and HI tests contained about 400 μg. of egg albumin per ml. As 0.5 ml. of the virus were used at a 1/80 dilution for each test, 2.5 μg. of egg albumin was available to react in the CF test with egg antibody which might have been present in the serum sample. In order to detect anti-egg antibody in these sera, CF tests were

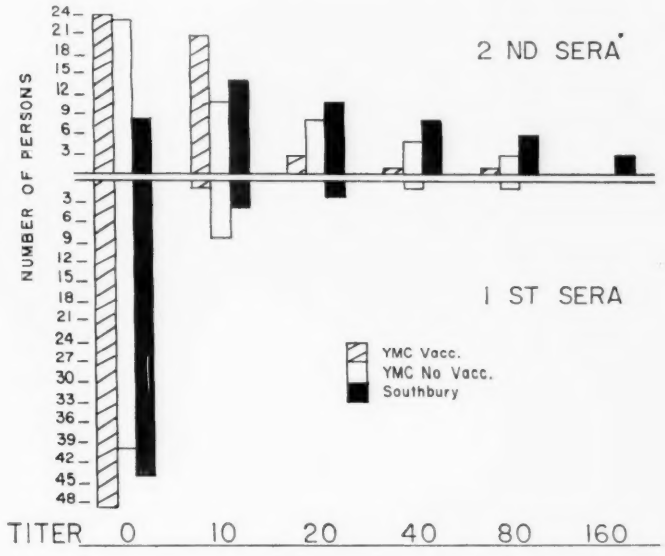

FIG. 1. Complement-fixation titers on the sera from the 150 subjects.

performed on the above 14 sera from vaccinated persons (2 with influenza-like illness, 12 without), and on a control group comprised of the 14 YMC unvaccinated subjects who also showed only a CF rise (Tables 3 and 4). In a preliminary 'checker-board" assay employing dilutions of egg albumin and dilutions of a calibrated rabbit antiserum, it was found that about 0.0625 μg. of albumin represented an optimal quantity of antigen for CF. Using this amount in 0.5 ml., CF tests with all 28 sera were negative. It therefore is indicated that the positive CF tests with the viral antigen were due to specific anti-viral antibody.

Tests were performed to investigate the possibility that those people whose blood showed only a CF rise were responding to an infection with an A or A′ influenza virus rather than the Asian strain. All of the 39

sera showing only an increased CF titer were tested with PR8 (A) and FM1 (A') influenza viruses by the HI test. There was one individual reporting influenza in the YMC unvaccinated group who had a fourfold rise with the FM1 virus, one individual in the Southbury group also reporting influenza who had a twentyfold rise to the same virus, and one individual without influenza in the YMC vaccinated group who had a four-

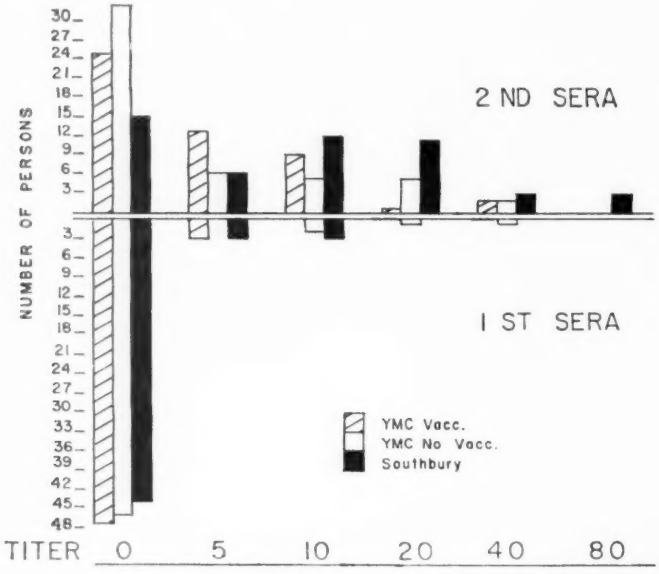

FIG. 2. Hemagglutination-inhibition titers on the sera from the 150 subjects.

fold rise to the PR8 virus. None of the other 36 paired sera had a significant rise with either of these viruses. The results indicate that it is likely that the increased CF titer with Asian antigen was due to Asian influenza in the great majority of cases rather than to another A or A' influenza virus.

Graphical representations of the titers obtained with the first and second serum samples are shown for all three groups by both HI and CF tests in Figures 1 and 2. The number of subjects demonstrating the various titers is shown at the left, with the first sera reading downward, and the second sera upward from the central line. Where an endpoint fell between two of the established serum dilutions, it was included in the next lower

titer for purposes of graphing. A titer of 15, for example, is included in the group showing a titer of 10.

The titers of the first sera are well concentrated at the left of the graph, with only a few showing significant levels of reactivity. Titers of the second sera are distributed more widely, signifying an immunological response due either to the vaccine or to contact with influenza on a clinical or subclinical basis. It is seen that the Southbury group had the highest titers, perhaps a reflection of the severity of the epidemic in this group. Also to be noted in Figure 1 is the great number of vaccinated people reacting with a low CF titer and the almost complete absence of anyone in this group with high CF titers. However, in both the CF and HI results one may see that there is a significant number of people showing no reactivity with the second serum.

Of the few subjects showing an initial titer by either or by both tests, there was a total of 12 in the YMC unvaccinated group, 4 in the YMC vaccinated group, and 11 in the Southbury unvaccinated group. In the YMC unvaccinated, the 4 HI titers ranged from 10 to 40, and the 10 CF titers from 10 to 80. In the YMC vaccinated group, all 3 HI titers were 5 and the CF titer was 15. In the Southbury population, the 6 HI titers ranged from 5 to 10, and the 6 CF titers, from 10 to 30. A problem of interpretation is raised here due to the fact that some of these findings may represent the presence of antibody, while some may have been due to the presence of a nonspecific inhibitor. However, of interest in this regard is the history taken on the two Yale groups before the first blood was drawn; no such history was available for the Southbury group. This shows that of the 12 unvaccinated persons showing an initial titer, 6 reported suspected clinical cases of Asian influenza before the first bleeding. The 2 who showed an initial titer by both CF and HI were among this group of 6. There were 4 who had reported suspected influenza-like illnesses before the first bleeding who did not show initial titers. In the YMC vaccinated group, 5 reported suspected influenza before the first bleeding. Of these, only one had an initial titer.

DISCUSSION

Although the number of individuals followed in the present study was relatively small, the results in terms of clinical attack and serological response were sufficiently clear to permit certain general conclusions. The attack rate in vaccinated individuals was strikingly lower than in unvaccinated persons (Table 2). Thus, it may be concluded that "protection" was afforded by a regimen consisting of two 0.1 ml. intradermal injections

of monovalent Asian influenza vaccine containing 200 CCA units per ml. It would seem prudent to avoid expressing this "protection" in numerical terms since virus isolations were not performed and constant clinical surveillance of all subjects was not possible.

Of equal interest were the divergent patterns of serological response manifested in all three study populations (Tables 2, 3, 4). The results of the CF and HI tests on paired sera showed that only 6 vaccinated and a

TABLE 3. ANTIBODY MEASUREMENTS IN PERSONS WITH INFLUENZA-LIKE ILLNESS

	Y.M.C. Vaccinated	*Y.M.C. Unvaccinated*	*Southbury Unvaccinated*
Antibody rise by both CF and HI tests			
threefold rise	1/3	2/20	16/33
fourfold rise	1/3	1/20	14/33
Antibody rise by HI test *only*			
threefold rise	0/3	1/20	3/33
fourfold rise	0/3	0/20	3/33
Antibody rise by CF test *only*			
threefold rise	2/3	13/20	9/33
fourfold rise	0/3	10/20	6/33

total of 26 unvaccinated persons developed antibodies adequate to cause a significant rise by both test procedures. In contrast, there were 60 persons who showed an increase in titer by one serological test without a corresponding change in the other test. Of these, there were 39 persons (14 vaccinated and 25 unvaccinated) who had an increase in titer by the CF test only, and 21 persons (8 vaccinated and 13 unvaccinated) who showed an increase solely by the HI test. An interpretation of these results became of vital importance in the selection of serological criteria for the diagnosis of Asian influenza. On the basis of classical experience with the serological characteristics of influenza, it seemed justifiable to diagnose those 32 persons with a rise in both the CF and HI tests as having Asian influenza. Similarly, it is probable that the 21 persons with increased HI titers experienced contact with Asian virus. However, the relatively large number of persons with only a CF response presented difficulty in inter-

pretation. This necessitated ancillary investigation along two main lines in order to clarify the relationship of the complement-fixing antibody to Asian influenza.

The increase in CF titer in the 14 vaccinated persons could, of course, have represented antibody formed in response to the egg material in the vaccine. This seemed unlikely since quantitative complement-fixation tests with egg albumin were negative with paired sera from these persons.

TABLE 4. ANTIBODY MEASUREMENTS IN PERSONS WITHOUT INFLUENZA-LIKE ILLNESS

	Y.M.C. Vaccinated	*Y.M.C. Unvaccinated*	*Southbury Unvaccinated*
Antibody rise by both CF and HI tests			
threefold rise	6/47	2/30	6/17
fourfold rise	2/47	1/30	4/17
Antibody rise by HI test *only*			
threefold rise	8/47	6/30	3/17
fourfold rise	7/47	6/30	2/17
Antibody rise by CF test *only*			
threefold rise	12/47	1/30	2/17
fourfold rise	3/47	0/30	1/17

Secondly, the increased CF reactivity might well have represented a cross-reaction of Asian virus with antibody against a related A or A′ influenza virus. Since the serological results represented an increase in antibody only during the study period, it would be necessary to assume that the 14 vaccinated and the 25 unvaccinated persons, or 26 per cent of the entire study population, had *non-Asian* influenza during a presumed Asian epidemic. In order to investigate this possibility, paired sera from these 39 individuals were titrated for HI antibody using the PR8 (A) and the FM1 (A′) strains of virus as antigens. Only three paired sera showed a rise in titer. Thus, one is left with the general conclusion that the results with CF tests were essential in estimating the extent of the current epidemic. In fact, the CF results were of greater relative value than were the HI tests. This was apparent from the fact that more individuals developed a significant increase in CF antibody than in HI antibody, both

in the vaccinated group and in those presumed to have had the disease. The magnitude of the rise of CF antibody appeared to have a direct relationship to the severity of the clinical illness. This conclusion is based on the Southbury population in which the highest CF titers occurred in those persons showing higher temperatures and more severe symptoms. In contrast there was no such relationship between temperature and the HI response.

The application of these serological criteria to those unvaccinated persons without clinical symptoms provided definite information on the subclinical or asymptomatic attack rates. It was of particular interest that the incidence in the YMC group, 9 out of 50, was essentially the same as that

TABLE 5. THE PERCENTAGE OF CASES OF ASIAN INFLUENZA WITH ELEVATION OF TITER BY CF AND/OR HI TESTS

	Total CF increased*	*Total HI** increased*	*Both CF and HI increased*	*CF only*	*HI only*
Jensen and Hogan[4]	76.4	61.8	38.2	38.2	23.6
Yale Study	80.0	61.5	41.5	38.5	20.0

* Either alone or with HI.
** Either alone or with CF.

in the Southbury group, 11 out of 50. This is in contrast to the serologically confirmed clinical attack rate which differed in the same two groups, i.e., 16 out of 50, and 28 out of 50, respectively. Thus, about 20 per cent of all unvaccinated persons presumably had asymptomatic Asian influenza while an additional 44 per cent had clinical attacks.

The combined subclinical and verified clinical cases gave an attack rate of 50 per cent for the Yale unvaccinated group and 78 per cent for the Southbury patients. The greater "virulence" of the infection in the institutionalized group also was reflected by the fact that 91 per cent of the cases occurred within a three-day period. In contrast, the onset of clinical symptoms in Yale personnel occurred more or less evenly over a two-week period.

The serological findings in the vaccinated individuals must be interpreted independently of the above considerations. While it is true that the increased titers in the 26 persons without symptoms could have represented asymptomatic infection, it is more likely that these responses were a direct consequence of vaccination with viral antigen. The possible occurrence of subsequent subclinical infections was not determined since

blood samples were not drawn unless clinical symptoms were reported. It is of interest that the results in the 65 persons serologically diagnosed as Asian influenza in the present study are remarkably similar to the findings of Jensen and Hogan[4] on 123 cases of Asian influenza diagnosed by virus isolation (Table 5).

SUMMARY

Three groups of 50 persons each were followed during the main duration of the Asian influenza pandemic of 1957. One of these groups was vaccinated against Asian strain influenza and two were not; the vaccinated group and one of the unvaccinated groups were comparable as to residence, contacts, age, etc. Paired sera from each participant were analyzed by both the complement-fixation and hemagglutination-inhibition techniques, but no attempt was made to isolate influenza virus.

The serologically confirmed clinical attack rates for the groups were: one out of 50 for the vaccinated group, 16 out of 50 for the comparable unvaccinated group, and 28 out of 50 for the other unvaccinated group. Significant antibody rises occurred in 27 out of the 50 in the vaccinated group, presumably due to the effect of the vaccine. In the comparable unvaccinated group, presumed subclinical infections occurred in 9 persons, and in 11 individuals in the third group. The combined subclinical and verified clinical cases gave an attack rate of 50 per cent for one unvaccinated group and 78 per cent for the other. On the other hand, no antibody rise occurred in only 11 of the total of 56 reported clinical cases.

Differences were observed in the results of the CF and HI tests. Some individuals showed increased titers in both serological tests, a few had a rise by HI only, and many showed a response by CF only. Ancillary tests with the latter sera excluded as responsible factors either an egg contaminant in the vaccine or a cross reaction with another A or A′ influenza virus. The serological results indicated that neither the HI nor CF test alone was sufficient for serological diagnosis of Asian influenza, and that diagnosis was more often made when both of the tests were used together.

ADDENDUM

A more recent finding which occurred after the conclusion of the formal study is worthy of mention. During the last two weeks of January and the early weeks of February 1958, another influenza-like epidemic struck the Yale Medical Center community, with the second-year medical class principally involved. Many of these students were subjects in the original study. The symptoms were typical of influenza, with some tem-

peratures as high as 104.5° F. The highest incidence appeared to occur in the vaccinated group. From some of these patients, throat washings were obtained during the acute stage of the illness, and, as hemagglutinating agent, presumably Asian influenza virus has been isolated from several.

In a verbal check of 147 of the original 150 subjects, 37 reported influenza-like illnesses in this second epidemic. Fourteen were from the original YMC unvaccinated group, and 5 of these had had serological evidence of influenza (clinical or subclinical) during the first epidemic. Of the five, two reported clinical influenza symptoms during both epidemics. In the original YMC vaccinated group, 25 reported influenza-like illnesses during the "second wave," and of these 25, 13 had shown a serological response during the original study. Of the 37 newly reported cases, 4 in the YMC unvaccinated group and 22 in the YMC vaccinated group were members of the second-year medical class. No influenza-like illnesses have been reported since the autumn of 1957 among the 50 Southbury unvaccinated subjects.

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GEORGE A. SILVER*

Division of Social Medicine, Montefiore Hospital, New York City

BEYOND GENERAL PRACTICE: THE HEALTH TEAM

In a group of articles published within the past few years[5,7,8] renewed effort was made to provide status for the general practitioner by extending his training and furnishing him with a more attractive job description. It is the purpose of this article to elaborate the thesis that it is not possible to restore the general practitioner, because of the passing of an era and its social setting, nor is it even desirable in view of vast changes in medical science and knowledge; rather, a new and more realistic format for the provision of medical services which were formerly the general practitioner's rsponsibility is needed and such a program is here described.

The general practitioner who knew a community inside and out, who encompassed all existing medical knowledge and skills, who was able to diagnose and minister to physical and emotional illness—from medical training partly, but more from intimate association with the people he ministered to—became obsolescent at the turn of the century. The personal, neighborly figure was attacked, in rapid succession, by the scientific advances of medical knowledge (which made it impossible for one individual to encompass the whole of medical knowledge and skill), by the reformulation of medical education on a scientific basis, and by the transformations in American social life incident upon the closing of the frontier: mechanization, industrialization, urbanization, and depersonalization. And if this was not enough, the internal revolution of medical care, occasioned by the above, removed the locus of definitive medical care to the hospital, thereby institutionalizing medical service and freezing the general practitioner out of the main stream of both care and learning.[22] Hospitals require staffs of specialists, and for what speciality is the general practitioner equipped? He can only do less than a specialist in any specialty. With the emphasis on standards of training and experience, it would be unfair to patients to offer less well-trained, or less experienced general practitioners as specialists on a specialized service. This would not be acceptable to the house staff, the doctors in training, any more than it would be to the specialists.

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* Chief, Division of Social Medicine.

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In fifty crowded years the extensive changes in American life demanded changes in the pattern of medical practice. But for reasons examined more in detail by sociologists elsewhere,[22, 24, 25] the form of medical practice has changed very little. Evidences of the trend to change, and the direction, are present. For example, specialization has come and is increasing. The percentage of medical school graduates limiting their practice to a specialty increased from 30 per cent in 1930 to 63.3 per cent in 1940.

General practitioners are inadequately trained to carry the new role in the increasingly scientific practice of medicine, at the same time that they are failing in the old role because they are improperly equipped to offer the guidance and support that the kindly "family doctor" dispensed

TABLE 1. PERCENTAGE OF PHYSICIANS BY TYPE OF PRACTICE AND YEAR OF GRADUATION FROM MEDICAL SCHOOL[23]

Type of practice	*Year of graduation*					
	1915	*1920*	*1925*	*1930*	*1935*	*1940*
General practice	22.5	23.8	25.1	31.5	25.0	23.4
Special attention to a specialty	35.6	40.4	40.5	37.9	18.2	12.0
Limited to a specialty	40.9	35.0	34.0	30.4	55.1	63.3
Not practising or not specified	1.0	0.8	0.5	0.3	1.7	1.3

instead of scientific medicine.[2] General practitioners are increasingly barred from the main site of medical practice, the hospital, and thus from improving, or even maintaining, the level of professional skill and knowledge they brought away from medical school five, fifteen, or twenty-five years ago. As one editorialist said, approvingly, " . . . the patient today may be cured of a once fatal illness by an expert whose name he didn't quite catch, instead of dying with his old family doctor sitting loyally at the bedside."[23]

Available evidence indicates that physicians are abandoning general practice for specialized practice and abandoning the rural areas in which the sociological base for continuing utility of this type of practice still remains[9] (see Table 1[23]). The average age of physicians in rural areas is considerably higher than that of physicians in urban areas[2, 8, 9] (see Table 2[23]). And finally, general practice does not pay nearly so well as specialized practice (see Table 3[22]).

The presidential addresses, departments of general practice,[8] academies of general practice, and solicitous editorials regarding moribund general practice[13, 18] do have a utility in the current scene. In a sense they offer solutions, though of a transitory kind. While declining in numbers and prestige, general practitioners do exist in their thousands. And short of

a revolutionary change in medical organization and/or methods of payment, they must continue to exist. Consequently, any effort to comfort the general practitioner in his role and to improve professional standards will be a service to him as well as to the community he continues to serve.

But it is important to recognize that this situation and these solutions are *transitory*. Increasing the years of training before a physician is allowed to practice is an excellent solution, but the content of the training should reflect the new situation and the new needs. Collings and Clark,[7] for example, concern themselves with creating a semi-specialist in a half dozen fields (which is possibly more difficult and certainly less attainable than accepting outright specialization and encouraging it), modifying practice in other directions to recapture the needed social role of the family doctor.

TABLE 2. TREND OF PHYSICIAN SUPPLY[25]

	Physicians per 100,000		
	1923	*1938*	*1940*
Counties having cities of 50,000 or more	155	175	180
Counties having cities of 2,500 to 49,999	120	100	100
Counties having no urban place	90	70	65

In that case, what of the "family doctor"? Who will see the patient in the first instance and determine if the complaint is minor or major? Who will refer cases to the specialists for more complex and precise diagnosis or treatment? Who will collate the reports as they come in? Who will adjust the *precise* "scientific" reports or findings to the patient, that imprecise person of infinite variability? Who will be so intimately related to the family as to know the interpersonal problems, assess them in relationship to the complaints or symptoms, and provide the support and guidance that probably does more to determine the duration or severity of an illness than the specific treatment? Who will carry on the day-to-day psychosomatic practice? Who?

As a Crown Council, on the death of a monarch, meets to arrange for an orderly succession, so it is the responsibility of medical educators and administrators to provide a system of organization and program of education to provide replacements for the defunct general practitioner.

These comments are not intended to disparage the general practitioner as understood by patients and doctors. The decline of this worthwhile social figure has had a damaging effect on patient-doctor relationships and

may bode even worse for the future. The question at issue is whether something meaningful in the person, or the practice, can be salvaged.

Since general practice is neither attractive to physicians[25] nor lucrative,[22] nor by present standards adequate to the needs of patients,[2, 23] perhaps various approaches to possible solutions should be tried in order to gain the experience necessary to recommend changes. After this, it will still require adjustments for students and practitioners and probably wholesale re-education of the patient population toward acceptance of any proposal, no matter how carefully tested.

Group practice is an obvious solution to the scientific overgrowth of medicine. Some of the previous strictures mentioned above lose their

TABLE 3. MEAN NET INCOME OF PHYSICIANS BY TYPE OF PRACTICE—1949[23]

	Independent practice	*Salaried*
General practice	$ 8,835.00	$6,281.00
Partly specialized	11,758.00	
Fully specialized	15,014.00	8,884.00

force when the complex and difficult sciences of modern medicine are broken up, and groups of specialists can then be brought to bear on the problems of disease and treatment. A number of excellent reviews of the need for and potentialities of group practice exist.[4, 16, 20] However, at bottom, the problem of the family doctor has still to be faced. In a group practice unit, composed of specialists, what will his specialty be? Will he do a little less of most specialties than the specialists? This is the same problem faced in hospital staff privileges. It is hardly fair to the patient, who is entitled to the best surgical care for *all* surgical conditions, not just some, the best pediatric, obstetrical, dermatological, and so on. What, then, should be the role of the family doctor? How will he be trained, what competence will he have, and how will he carry on such diverse activities as a family doctor must? It goes without saying that the people (the patients) continue to want and need a doctor with the qualities of the old family doctor. They want to be considered "as a person,"[27] as Canby Robinson so neatly puts it.

The experience recorded below is not intended to fix the limits of the changes necessary. This is *one* experience, a demonstration of *one* type of method for meeting the situation. There will, of course, be situations in which such a high degree of organization will not be possible at the present time. Hospitals, laboratory facilities, and adequate transportation

are lacking in many rural or semi-rural areas. For these, another type of solution can be and is being worked out. For example, the Rip Van Winkle Clinic is experimenting with outpost doctors in a group practice unit.[9] Let us keep in mind, however, the vast number of people who *do* live in urban areas in which a practice as described below is feasible.

This introduction should serve as the background for the presentation of the wholly new type of family medical practice postulated here to fill the gap left by the disappearing general practitioner. Under the joint auspices of the Community Service Society, the Columbia College of Physicians and Surgeons, and the Montefiore Hospital, the Family Health Maintenance Demonstration is being carried on. A fairly complete statement of the origin and aims of this program, as well as a description of the roles of the participants, will be found in *The family health maintenance demonstration.*[21] In brief, this program was inaugurated "to determine what services can reasonably be added to a comprehensive medical care program which would result in favorably influencing the health of the families concerned."[5] In order to provide preventive service, evaluations were first carried out on 150 presumably normal families selected at random from among 8,000 families subscribing to the Health Insurance Plan of Greater New York[1] who were members of the Montefiore Medical Group. After determining need, both the medical care and the health promotion activities on behalf of these families were carried on by the Demonstration. For the purposes of this paper, I would like to pass over the research aspects and information-collecting side of the Demonstration and emphasize the method of providing service.

Preventive and therapeutic services are provided by a "health team" composed of a physician trained in internal medicine, a psychiatric social worker, and a public health nurse. For children under 13, the evaluation, medical care, and preventive responsibility are lodged in a trained pediatrician.

The team operates by dividing responsibility, delineating individual roles, and accepting each other's professional competence. By holding to the democratic team structure, conflict is avoided, and the procedure rendered relatively frictionless.[10, 11] The doctor is responsible for the physical disease. The public health nurse is responsible for collecting information about housing, nutrition, health practices, school and occupational adjustment, and the recreational aspects of family life. The social worker concerns herself with interpersonal relationships and adjustments, the emotional problems of family living. Obviously, in the preventive area there will be overlapping of interest and competence, as, for example, in child growth and development, where all have a stake.

The families who enter the Demonstration are examined by the team, according to this scheme, to provide a body of information that can be used as a base both for the research and the services to the family. Some of this information is obtained in interviews in the office, some at home. After studying a family according to their schedules, the team meets and discusses findings. The individual team members sort out impressions as they are modified by the new information gained from the others. Out of this emerges a plan for the family. This in turn is discussed with the family. The team member with a responsibility in a given area takes up the preventive or therapeutic recommendation and follows through. In the overlapping areas the team member with whom the family seems most comfortable takes over.

After this conference the family may call on only one of the team members for service, following the plan and using the nurse or social worker or physician for the physical or emotional condition found at the preliminary evaluation. Later, other team members may be called upon by the one working with the family for additional care or for assistance with a new problem. In any case, any and all members of the team are ready and may be called upon to help. At the same time routine conferences are being held by the team so that information is exchanged and they apprize one another of developments. A unit record for the family makes it possible for all team members to be informed. This compound replacement of the family doctor, the health team, is aware of all the nuances of strength and weakness in the family structure and is prepared to cope with problems. Additional opportunities for discussion and interchange of opinion and information are offered at the organized group educational meetings carried on by team members as well as in the casual contacts at the office. When a mother brings a baby to the pediatrician for a routine check-up, she will have an opportunity to see the social worker or nurse, or her own physician, and say a few words, or get an insight into some other matter that troubles her, or some question she may have in her mind. Every contact is an opportunity to tap the knowledge and skills of all the members of the team, because the intercommunication of the team members leads to exchange of skills and interests.

It goes without saying that such a team offers unparalleled opportunities for preventive medicine. Just as group practice provides for the entry of specialized care into family practice, the health team with its increased area of contact provides for preventive service, particularly in the emotional field. The initial evaluation offers the base, the frequent contacts, the educational medium for preventive practice.

Considerable discussion could no doubt be engendered as to why social worker and nurse were chosen as the physician's teammates. Why not one or the other? The thought that went into the selection is no doubt evident in the description of the duties. In the past fifty years each of these professions has established a therapeutic area,[15, 17, 19, 31] and the education for this role is time-consuming and precise. In establishing preventive roles for both, the therapeutic role played heretofore had to be considered. Perhaps a polyvalent associate of the physician *can* be developed, some one with the characteristics of both public health nurse and social worker. Of course, it may be considerably harder to develop a new type of professional person than to use the expanded services of existing professional people.

Who is this "internist" who participates as a partner with the social worker and public health nurse on the health team? What is his training, what is his actual job as a doctor? Briefly, he is trained as a specialist in adult medicine, with two to five years of hospital experience after graduation from medical school. He is eligible for the Board of Internal Medicine. He cannot and should not deliver babies, refract eyes, set fractures, remove tonsils, or diagnose and treat the ills of infants. But he does offer the round of medical services to adults in the home, office, and hospital which a trained medical specialist can provide. This "internist" is not the classical "diagnostician" or "consultant" who is called in to give an occasional expert opinion. He is the family's personal physician and has the training and experience to diagnose and treat the simplest or most complex of medical conditions. The classical consultant in medicine will find less place for application of his skills, too, since the internist described here will be much less in need of help or support to handle cardiac complications, diabetes, or thyroid disease. And the family internist will, by making both house calls and hospital visits in addition to office care, provide the continuity of care so essential to good medical service.

This family internist member of the team sees medical practice as a satisfying union of the application of his skills and the rewards therefrom. He looks forward to staff advancement on the hospital medical service to which he is attached, teaching and learning through teaching, participating in modest clinical research and study—a life of continuous professional growth. His salaried position in a medical group offers him satisfying freedom from sharp competitive practice and the need to drive for financial goals. All of his energies can be focussed on patient care, mediated through his personal attention to patients and his participation in team activities.

The health team is supported by two consultant bodies. On the one hand there is a group of medical specialists: the surgeons, obstetricians, ophthalmologists, and so on, the specialists who are part of the Montefiore Medical Group. To them will be referred patients with the diagnostic and therapeutic problems an internist or pediatrician could not be expected to handle. But the health team collates the information received from the consultants and makes the decision as to the appropriate therapy (except in emergencies, of course) just as a family doctor would.

On the other hand, a group of consultants reflecting the *added* aspects of modern medical service advise the team. A psychiatrist, psychologist, health educator, and social scientist comprise this group. The health educator helps the team organize and run health promotional activities: group discussions, educational films, advice on the selection of health educational materials. The social scientist is concerned with team-patient and intra-team relationships. The psychologist is responsible for psychological testing, the results of which will verify or supplement the team evaluations in the area of emotional difficulty or interpersonal functioning.

The psychiatrist plays a part which underlines the basic value of the team as a modern replacement for the family doctor. He is charged with providing information and training in his field so that the *team* can accept responsibility for separating minor from major emotional disease ("major" being severe psychoneurosis or psychosis) and for referring the individual with major emotional illness to an appropriate agency. Minor difficulties, in this rather broad sense meaning the ordinary stresses of family living and the day-to-day problems that may require professional advice and guidance, are handled by the team itself. In routine conferences the psychiatrist provides supervision and either general or specific advice, without dealing with the patient directly.

I do not mean to exaggerate the psychiatrist's role or importance to the team operation. But here is the kind of situation in which the health team helps families in the same way the family doctor was able to help them, a factor regrettably missing from large areas of general practice today. Furthermore, by removing a good bit of what might ordinarily find its way to the psychiatrist, the health team allows that specialist to devote his scarce skill to those who are seriously ill and who are so much more in need of him. Such a program as that recommended by the Commonwealth Fund[20, 34] for helping the general practitioner to establish himself in this psychotherapeutic area and for providing the added skill he needs to reduce the tremendous burden of emotional disease and unhappiness can also be put to effective use by the health team.

I should now like to touch upon another moot and presently shifting area—medical education. The next development in medical education could well grow out of this idea of a health team. Already, with declining ward and out-patient populations and growing medical insurance coverage, the medical school must look to new sources of teaching material. In some places the shift is evident in the new organization of out-patient teaching services.[18, 20, 29] Certainly, learning how to provide medical care and to practise preventive medicine will be easier and more rewarding within the framework of a health team.

Such an organization obviously requires a delicate financial and contractual arrangement. Group practice with prepayment is feasible, as has been demonstrated by the Health Insurance Plan of which the Montefiore Medical Group is a part. To add the services of a health team is to increase the cost of health insurance surprisingly little. Our study is not yet finished, so precise information as to cost will not be available for a few more years, but at the moment a guess would be that a 10 or 15 per cent increase in the cost of health insurance is all that would be necessary.

To conclude, I have attempted to show that scientific advance is inevitably forcing specialization and institutionalizing medical care, and sociological changes which are hopelessly isolating the doctor from the community are making the general practitioner obsolete. Efforts to restore the general practitioner to his preëminent position are doomed to failure in the long run, although temporary measures are justified because individuals will continue in such practice for a significant number of years, and their professional skill should be enhanced in every way possible.

The growth of group practice on a prepayment basis is proceeding in this country at a regular, though slow, rate. This growth should be fostered and the rate accelerated by the active efforts of the medical profession. There are many reasons why the profession itself should be boldly involved in this, not the least of which is that group practice is the vital substrate on which the health team replacement for the family doctor can be built.

A description of the proposed health team has been given, illustrating the part it plays in providing medical care for those families participating in the Family Health Maintenance Demonstration at Montefiore Hospital. It is shown how, within the framework of group practice, such a team, composed of a physician (trained and qualified internist for adults, trained and qualified pediatrician for children under 13), public health nurse, and psychiatric social worker, functions in providing the diagnostic, preventive, and therapeutic services families need in both the physical and emotional area. The team is supported by a medical group practice unit for spe-

cialized medical services and a consultant group composed of psychiatrist, psychologist, and social scientist to help discharge the other aspects of its functions. The psychiatrist's role with such a team is to provide education, supervision, and advice for the *team.*

The team provides advice, guidance, and support in the ordinary emotional stresses of the family, attempting through individual and group educational activities to lessen present and future difficulties. Severely psychoneurotic or psychotic family members are referred to appropriate agencies for care.

The health team is recommended as a method for replacing the advantages the general practitioner formerly offered and which the community still needs. Organization of medical care around such a team in a group practice unit, and medical education around such team practice should be considered.

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GEORGE J. FRIOU*

Medical Service of the Veterans Administration Hospital, West Haven, Connecticut, and the Department of Medicine, Yale University School of Medicine

CLINICAL APPLICATION OF A TEST FOR LUPUS GLOBULIN-NUCLEOHISTONE INTERACTION USING FLUORESCENT ANTIBODY**

In studies reported elsewhere we have demonstrated by the fluorescent antibody technique that serum of patients with disseminated lupus erythematosus contains a globulin factor with a marked affinity for nuclei.[7,8] In further investigation of this reaction it was shown that the component of nuclei involved was in the nucleoprotein fraction.[4,5] During this study a method for titration of this activity of sera was developed which utilized a nucleoprotein extract of calf thymus. With this method it was possible to obtain reproducible titration of activity of sera in a more refined system than that involving intact nuclei. A preliminary study indicated that an extensive survey of the occurrence of this factor in human sera would be of interest.[4] These results are the subject of the present report.

MATERIALS AND METHODS

Fluorescent antibody technique. Complete details of this technique have been reported elsewhere and will therefore not be described here.[1,8] The method utilizes a fluorescent dye, chemically bound to antibody, as a visual tracer or stain of a specific antigen. An indirect procedure was employed in application of the technique to this problem. Nucleoprotein was first exposed to the serum being tested, and after excess serum was washed away, to fluorescent rabbit antibody for human gamma globulin. The preparations were then examined under the microscope with a powerful source of ultra-violet light. When fluorescence was observed, it indicated that human gamma globulin from the serum being tested was bound to the insoluble nucleoprotein.

Nucleoprotein. Calf thymus nucleohistone was prepared by the method of Crampton, Lipschutz, and Chargaff.[2] After preparation it was dissolved in distilled water adjusted to pH 7.0 by addition of $NaHCO_3$ to approximately .0004 M. This material was divided into aliquots sufficient for several days' work and frozen at —60° C. When prepared and stored in this way the material remained useable for several months, after which noticeable deterioration had occurred. As needed for testing a small quantity was thawed and mixed with an equal volume of 2 M NaCl, forming a clear viscous solution.

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* Chief, Infectious Diseases Section, Medical Service VA Hospital, and Assistant Professor of Medicine, Yale University School of Medicine.

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Drops of about .05 ml. volume were placed on glass slides and fanned until dry or, during humid weather, placed in enclosed trays over Drierite. Nucleoprotein spots prepared from this concentrated salt solution were found to be the most satisfactory preparations for this work. The homogeneous character of the solution facilitated handling, and the crystalline pattern resulting from drying of the salt gave contrast which aided in evaluation of fluorescent staining. When thoroughly dry, slides were dipped in 0.15 M NaCl to remove excess salt. After draining, excess moisture was blotted from the edges of the slide. Processing with serum and fluorescent antibody was then carried out.

HUMAN SERA

Sera from 369 individuals were tested for their affinity for nucleohistone spots. Most of the sera were from patients at the Grace-New Haven Community Hospital, New Haven, and the Veterans Administration Hospital, West Haven, Connecticut. A few specimens were obtained elsewhere. Sera were frozen at —20° C. from the time received in the laboratory until tested. Results of tests with intact nuclei using some of these sera were the subject of an earlier report.[8]

The categories of patients tested are indicated in Table 1. In collecting the sera an attempt was made to include certain groups which seemed particularly important for purposes of comparison. In addition, large numbers of sera from miscellaneous unrelated diseases have been included.

The patients with disseminated lupus had been diagnosed by the usual criteria. In each case there was agreement on the diagnosis by several competent observers. The L.E. test had been positive sometime during the course of the disease in all except three of these patients. The diagnoses recorded were established without knowledge of results of the tests with fluorescent antibody.

Fluorescent antibody test procedure. Nucleohistone spots, prepared as described above, were flooded with the serum specimen being tested and placed for 30 minutes in a moist chamber at room temperature. After this they were washed twice for five minutes each with buffered saline. They were then flooded with fluorescent conjugate at a 1 : 5 dilution for 30 minutes, washed again as above, drained and mounted in buffered glycerol under a cover slip. Slides were examined under the microscope with the filtered high intensity ultra-violet light source described elsewhere.

The diluent for all serum dilutions and washings in the steps outlined above was isotonic phosphate buffered saline at pH 7.0. Tests were done first with undiluted serum and at 1 : 16 dilution, followed by twofold serial dilutions over the range appropriate for determining the end point. To minimize bias during reading, the sequence of the dilutions was mixed in a manner unknown to the person reading the tests. Results were recorded as negative when green fluorescence was not observed, plus-minus (uncertain), and one plus to four plus, depending on the brightness of fluorescent staining. The highest dilution giving at least a one plus reaction was considered the titer of that particular serum. Certain sera gave weak and variable reactions (plus minus—one plus) when tested undiluted, and therefore only sera causing fluorescence at 1 : 2 or higher have been tabulated in final analysis of results. Except for the variable weak reactions in some tests with undiluted sera, results of repeated tests at different times on individual serum specimens were quite consistent. In 14 such paired determinations on individual serum specimens the same titer was obtained in 10, and a difference of one dilution in 4.

TABLE 1. AFFINITY OF 369 HUMAN SERA FOR NUCLEOPROTEIN

Diagnostic categories in which positive tests were encountered

Diagnosis	*No. tested*	*Positive*	*Diagnosis*	*No. tested*	*Positive*
Disseminated lupus erythematosus	35	35	Dermatomyositis	2	1
Rheumatoid arthritis	42	4	Hypersensitive drug reaction	16	1
Biologic false positive serologic test for lues	17	4	Syphilis	18*	2
Scleroderma	3	1	Neoplasm with metastasis	9	1

Diagnostic categories in which positive tests were encountered

Diagnosis	*No. tested*	*Diagnosis*	*No. tested*	*Diagnosis*	*No. tested*
Discoid lupus	5	Multiple sclerosis	5	Meningitis	4
Reynaud's disease	1	Bronchial asthma	5	Minor infections	8
Acute rheumatic fever	13	Bronchiectasis	5	Undiagnosed fevers	4
Acute glomerulonephritis	10	Pulm. tuberculosis	15	Pyelonephritis	5
Allergic arteritis	3	Sarcoidosis	2	Hodgkin's disease	3
Chronic glomerulonephritis	4	Brucellosis	1	Multiple myeloma	3
Nephrosis	3	Hyperglobulinemia	1	Chronic leukemia	4
Benign pericarditis	1	Infectious mononucleosis,		Myocardial infarction	6
Idiopathic myocarditis	2	ideopathic	4	Portal cirrhosis	12
Reiter's syndrome	1	Bacterial pneumonia	11	Hemochromatosis	1
Erythema multiforme	1	Atypical pneumonia	3	Others	81

* See text.

RESULTS

The diagnostic categories of the 369 patients whose serum was studied, and qualitative results of the tests are indicated in Table 1. Positive tests were obtained with all of 35 sera from patients with disseminated lupus erythematosus. Positive results were also obtained with sera of 4 of 42 patients with rheumatoid arthritis, 1 of 3 with scleroderma, 1 of 2 with dermatomyositis, 4 of 17 who had a chronic biologic false positive serologic test for syphilis, and 1 of a group with urticarial hypersensitive reactions to drugs. Of 5 patients with discoid lupus without clinical or laboratory evidence of disseminated disease, none was positive.

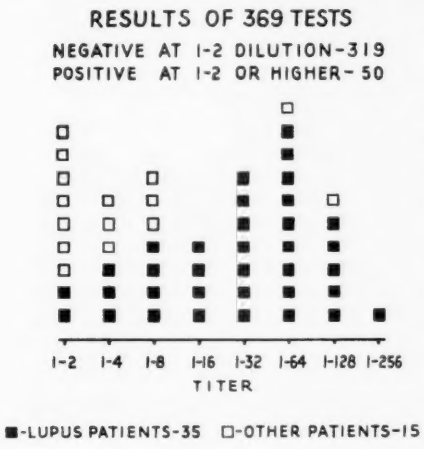

FIG. 1.

Among all other sera tested, 3 reacted with the nucleohistone. Two were in patients considered to have late latent syphilis. Review of these patients' records indicated that there was no definite history of syphilitic infection, and that the titer of activity in the test for syphilis was low.

Treponema immobilization tests had not been done, but it is possible that these represent biologic false positive reactions. The remaining serum which reacted in the test with nucleohistone was a patient with far advanced metastatic bronchogenic carcinoma. There were no features suggestive of lupus in this case.

Consideration of results of titration of the positive sera is essential for full appraisal of results. These are shown in Figure 1. Reactions by sera of patients not considered to have lupus, indicated by open squares in the illustration, were of relatively low titer. There were two exceptions, both of which were cases of particular interest. One was a young man with findings consistent with rheumatoid arthritis of four years' duration. For several months prior to the date of this test he had had intermittent slight hematuria and albuminuria. On examination he was found to have generalized lymph node enlargement and splenomegaly in addition to evidence of chronic joint disease compatible with rheumatoid arthritis.

Shortly after the date of this test he developed an episode of pleurisy on the right. L.E. tests at this time were negative. Recently he has suffered a second episode of pleurisy, this time on the left side. At the present time both the nucleohistone spot test and the L.E. test are positive. The diagnosis of disseminated lupus erythematosus is clearly established in this case. The second of these individuals was a middle-aged man with scleroderma of several years' duration without evidence of recent activity. He has had moderately severe thrombocytopenia and has also had intermittent abnormal urinary findings. Because of these features the diagnosis of disseminated lupus erythematosus was considered by many to be the proper diagnosis in this case, although the final decision must await further developments in the course of the disease. No other patients not previously considered to have lupus had high titers, and none of those with low titers had clinical features suggestive of disseminated lupus.

It has been indicated previously that many of the patients with lupus were in a remission of variable degree, either sustained spontaneously, or due to the suppressive action of prednisone. Detailed analysis of the clinical course in relation to titer of affinity for nucleohistone will not be described here. On the basis of the results of single tests, and a few individuals from whom repeated serum specimens were obtained, certain general statements can be made. It was evident that patients in remission of some duration tended to have low titers. Patients who were acutely ill, or had recently been so, had titers in the higher range. During the early weeks of therapy with prednisone, however, improvement in the condition of the patient was not necessarily accompanied by an abrupt fall in titer.

DISCUSSION

The data presented here indicate that measurement of this factor could be usefully applied in diagnostic evaluation of patients with the rheumatic diseases and related conditions. In this study the presence of the factor in high titer has invariably been associated with findings consistent with the diagnosis of disseminated lupus. It was not absent from the serum of any established case.* In considering patients with clinical findings suggestive of lupus, the finding of a high titer of this factor appears to be highly

* In data reported in connection with our study of the reaction of lupus sera with intact nuclei, a single serum was obtained that failed to react.[8] This specimen was from an individual in a long sustained remission under prednisone therapy. The serum had been stored in the refrigerator for 15 months before being received in this laboratory. This specimen was not available when the present tests were being done, but a more recent bleeding was positive at 1 : 4 dilution. Although the factor is relatively stable, it is felt that the activity of the first specimen may have been lost during the long storage period.

specific and the test useful as a means of establishing or eliminating disseminated lupus erythematosus as a diagnostic possibility. The finding of low titers in occasional patients with diseases closely akin to lupus requires that any conclusions regarding specificity be qualified. These individuals did not have other manifestations of lupus, however, except for a positive L.E. test in some instances. The complete natural history of lupus is often long, and it is well known that in some instances an isolated manifestation such as a chronic biologic false positive serologic test for syphilis,[12] or arthritis resembling rheumatoid arthritis,[9] may precede the complete clinical syndrome by long time intervals. The finding of low titer of the factor in serum from some of these patients does not establish the diagnosis of disseminated lupus in such a case. The observation is consistent with prevalent concepts of the disease, however, and further study of the occurrence of the factor in serum of patients not diagnosed as lupus may provide information on the relationship between disseminated lupus and these other conditions. The data suggest the interesting possibility that detection of the factor at low level in rheumatoid arthritis, or in other diseases, may be useful in anticipating future risk of occurrence of disseminated lupus.

It is attractive to reflect on the possibility that the factor may be implicated in the pathogenesis of this disease, especially in view of the recent emphasis on altered nuclear material among the histopathologic findings in lupus.[10] Evidence available at present does not indicate whether we are dealing with a cause or a result. The concept of lupus as a disease due to "auto-antibodies" has been popular in recent years. The factor under study is part of the gamma globulin fraction of serum proteins, and its properties are compatible with those of a heterogenetic antibody. Robbins, *et al.*, have recently reported complement fixation when sera from some patients with lupus are exposed to intact nuclei or DNA.[13] This observation provides additional support for such a concept. However, sera from a considerable proportion of such patients did not possess such complement-fixing activity. The full significance of these observations remains to be determined.

The connection between this factor and that responsible for the L.E. phenomenon is of considerable interest. In an early study Miescher reported that when serum of patients with lupus was incubated with nuclei, the ability to induce L.E. cells was eliminated.[11] With application of the fluorescent antibody technique to this problem it was possible to demonstrate more directly that under such conditions globulin is bound to nuclei.[6] In another report the procedure applied here was described and it

was demonstrated that absorption of lupus serum with nucleoprotein removes L.E. phenomenon activity and this factor simultaneously.[6] Presumably the factor detected by the method used here is the L.E. factor, and its reaction with nucleoprotein is the first step in the L.E. phenomenon. In data presented elsewhere it was demonstrated that all of these sera reacted with nucleoprotein spots although many failed to induce a positive L.E. test. The data indicated that among sera positive with the nucleoprotein spot test there was no clear relationship between titer of this factor and ability of a particular serum to induce L.E. cells.[5] A possible explanation for this finding may be found in recent observations of Finch and Detre,[3] who demonstrated that serum of most patients with disseminated lupus has a depressing effect on phagocytosis. Such an effect would tend to obscure any relationship that might exist between titer of a serum factor and induction of L.E. cells.

Experience with the fluorescent antibody technique until quite recently would indicate limited applicability as a generally used diagnostic test. There have recently been improvements in available standard optical systems for fluorescence microscopy. Methods of labelling of antisera with fluorescent dyes have also been simplified.[14] Furthermore, experience in this laboratory has indicated that fluorescence of spots of nucleoprotein may be determined by gross inspection with an inexpensive source of ultraviolet light. Other methods of detecting the reaction have also been investigated. A technique using iodine^{131} instead of the fluorescent dye as a label on anti-human globulin has recently been reported.[9] Experience with a modification of the latter procedure indicates that it is an accurate and sensitive means of measuring the factor in human serum.[6a]

SUMMARY

Sera from patients with a variety of human diseases have been tested for presence of a globulin factor which reacts with nucleoprotein. The tests were made, and activity of the factor titrated, with an adaptation of the fluorescent antibody technique. The factor was found to be characteristic of sera of patients with disseminated lupus erythematosis, especially when present in high titer. It was also present in low titer in occasional sera of patients with disease syndromes known to be closely related to lupus, especially rheumatoid arthritis and individuals with chronic biologic false positive serologic tests for syphilis. The possible significance of these findings is discussed, and use of this procedure as a diagnostic method considered.

ACKNOWLEDGMENT

The author is indebted to Miss Carmela Santarsiero for her loyal and able technical assistance. He is also indebted to physicians who generously provided sera for use in this study, including Drs. Halstead Holman, Charles Ragan, Charles Rein, and Paul Boisvert, and to Dr. Albert Coons for his advice and assistance in working with fluorescent antibody.

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PRESENTATION OF THESES OF THE CLASS OF 1958

May 22, 1958

A STUDY OF THE RELATIONSHIP OF EARLY SEPARATION FROM PARENTS TO SEX DIFFERENCES IN ADOLESCENT ADJUSTMENT IN AN INSTITUTIONAL SETTING. By Bruce H. Sklarew.

The study focuses on sex differences in adjustment within the context of an investigation of the effects of early separation on adolescents at the George Junior Republic. Contradictions in the literature on the effects of separation from parents may be partially clarified by considering previously unreported differences between boys and girls. The study attempts to evaluate the interaction of separation at various ages to certain described criteria of adjustment at the Republic.

Separated boys and especially those separated in the first three years of life demonstrate poorer adjustment than the nonseparated on the criteria most related to active nonconformity to standards—Court Offense Score and Run-Away Score. There are no essential differences between the two groups on Bank Accounts and Government Position Score, the "achievement-oriented" criteria. The nonseparated boys are conforming more than the separated ones on the General Adjustment Rating.

The separated girls, in contrast, conform to standards to a greater extent than the nonseparated on the "achievement-oriented" criteria-Bank Accounts and Government Position Score (strong trend). The girls separated in the first three years run away less than those not separated. There are no differences on the Court Record Score. On the General Adjustment Rating the separated girls tend to conform better than the nonseparated.

The second order sex differences reveal that separation is related to better adjustment for the girls than for the boys on Run-Away Score, Court Offense Score, and General Adjustment Rating. There are trends in the same direction for Bank Account and Government Position Score. The same sex differences are present for those separated in the first three or five years for Run-Away Score and Court Offense Score, and in the first five years for General Adjustment Rating. Thus for boys, separation is related to poor adjustment, as might be expected, but for girls separation is related to better adjustment.

These sex differences are discussed in terms of heightened aggressive impulses in boys and an increased tendency towards guilt and conformity to standards in girls. Other social and cultural factors are also considered.

In separated boys increased longings for passive gratification conflicting with the masculine role and their defense is acting out. Separated girls, in contrast, are able to accept and possibly sublimate these passive longings.

TOLERANCE, ANTAGONISM AND THE RELATION BETWEEN D-LYSERGIC ACID DIETHYLAMIDE AND MESCALINE. By George K. Aghajanian.

Interest in psychosis-inducing agents such as LSD-25 and mescaline revolves around the possible relation of these to the hypothesized "toxin" in schizophrenia. Although there are similarities between the drug syndromes

and schizophrenia, this fact does not establish the existence of a relationship at biochemical sites. Even if a drug could mimic a natural psychoses precisely, there still might be no similarity in the processes leading to the same end result. The primary goal in this study was to discover the nature of the relationship between the biochemical sites of action of LSD-25 and mescaline. This knowledge would provide a basis for exploring the biochemical factors, if any, that contribute to schizophrenia.

Our approach to the problem of determining biochemical relationship was through the techniques of cross-tolerance and specific antagonism. These are *in vivo* methods that can provide knowledge about relationships in sites of action. The experimental subject used was the rat. Drug effects were measured in a quantitative behavioral test (rope climbing). The rat attains tolerance to the behavioral effects of LSD-25 and this tolerance was found to occur similarly in rats with mescaline. Cross-tolerance experiments showed that LSD-25 confers protection against mescaline, but the reverse does occur. The existence of such unindirectional cross-tolerance provides partial evidence for some relation in sites of action.

In antagonism studies it was found BOL-148, an "inert" derivative of LSD-25, antagonizes the behavioral effects of the parent drug. Since this structural homologue presumably antagonizes at the LSD-25 biochemical site of action, antagonism of another psychosis-inducing agent by BOL-148 would provide presumptive evidence of a close relation in sites of action between LSD-25 and the other drug. It was in fact found that BOL-148 is an effective antagonist of mescaline, a drug with no previously known structural or experimental relation to LSD-25.

It is concluded from the cross-tolerance and antagonism experiments there is a very close relation between the biochemical sites of action of LSD-25 and mescaline, but that the sites may not actually be identical.

The choice of mescaline as the agent to be tested against BOL-148 was purely arbitrary *in so far* as its known biochemical relation to LSD-25. In this light it might be expected that BOL-148 would antagonize psychosis-inducing agents other than mescaline or LSD-25. Such an approach would provide a means for systematic classification of all such substances. Any agent not antagonized by BOL-148 probably does not act at the mescaline-LSD-25 sites. Furthermore, since serum from schizophrenic patients is claimed to induce effects in rats similar to those of LSD-25 and mescaline, if antagonism of such effects by BOL-148 occurred, there would be a strong suggestion of a chemical relation between the psychosis-inducing drugs and the hypothesized toxin of schizophrenia.

HUMAN INFERTILITY. By C. Lee Buxton and Anna L. Southam. New York, Paul B. Hoeber Inc., 1958. 229 pp. $7.50.

This book is a distillation of the authors' experience with human infertility—its prevalence, implications, diagnosis, and treatment. It is a useful practical guide for the physician who deals with this problem and includes detailed discussion of the techniques of investigation. There is an excellent chapter on endometrial interpretation by the late Dr. Earle T. Engle.

The authors are to be commended especially for an attempt to evaluate critically the results of current treatment. This is a uniquely difficult undertaking, since every infertility case involves at least two persons, each with physical variables, cultural and emotional attitudes, and psychological vagaries which affect anything that touches upon the procreative function. The difficulty is further compounded. Many couples who have no recognized reason for infertility never achieve a pregnancy, while other patients sometimes conceive in the face of formidable odds. In the treated patient success is usually ascribed to therapy; in the untreated it is accepted as an inexplicable act of God.

The authors have taken statistical cognizance of the acts of God, and the results are sobering. For example, complete tubal occlusion, demonstrated by salpingogram, is usually regarded as an insurmountable obstacle to conception unless surgically corrected. An analysis of the results of surgery showed a 14.6 per cent pregnancy rate after tuboplasty in 48 patients, though more than half of the pregnancies were abortive or ectopic (page 177). However, of 71 patients with tubal closure not treated surgically, follow-up revealed a pregnancy rate of 11.3 per cent (page 162). In the important area of infertility attributed to ovarian dysfunction the results of therapy are even more discouraging. The statistical advantage here lay with the untreated group (page 132). An impressive number of infertility patients conceived after history taking or discussion alone, or simple pelvic examination, or indeed after making an appointment for the initial visit! (page 17). It is not surprising that many strange remedies are reported to yield wonderful cures. The waters have long been muddied by our ignorance of what happens to the untreated patient.

This is not to say that investigation and treatment are fruitless. There are some spectacular successes in the treatment of Stein-Leventhal ovaries, and many other successes clearly attributable to treatment. These are gratifying, and make the effort worth while, particularly since the specialty is young and rapidly progressing and but lately graduated from armulets and incantations.

IRVING FRIEDMAN

VARIABLES RELATED TO HUMAN BREAST CANCER. By V. Elving Anderson, Harold O. Goodman, and Shelton C. Reed. Minneapolis, The University of Minnesota Press, 1958. 172 pp. $4.00.

For many years it has been assumed that an hereditary or at least a familial influence is present in the development of human cancer. This assumption has been based on poorly founded clinical impressions in most instances, but there have been several attempts to analyze the question on

a statistical basis. These latter studies have indicated that daughters and sisters of females with breast cancer had a significantly greater chance of developing cancer than persons in various control groups used in these studies. Unfortunately faulty planning and idea execution existed in so far as the control groups were concerned and it was on this basis that a study was started at the Dight Institute for Human Genetics of the University of Minnesota. This study was planned to overcome the faults of previous similar attempts to ascertain the role of heredity in the cancer problem. The present volume is a detailed report of this study in which 621 breast cancer patients were carefully interviewed from multiple viewpoints with emphasis on the choice of original patients and the completeness of information.

There is value of course in the scientific application of such fact finding, but perhaps more important are the clinical applications. The authors state that the study was designed primarily to answer the question: "Do relatives of breast cancer patients have an increased risk of developing cancer?" The query is answered from a voluminous mass of statistical material all of which is presented in the report. The final impression of the authors is that 7.4 per cent of the study group sisters would develop breast cancer before they die as compared with 4.2 per cent of the control sisters. Further, it was demonstrated that once a cancer has developed in one breast the risk of one developing in the other breast is about three times that for other women of the same age. The authors conclude that "it is very likely that genetic factors are involved in the etiology of breast cancer, but they are either so common in the population or depend so much upon environmental factors for expression that it is difficult to demonstrate their effect."

At the end of the book the authors suggest several areas which bear further investigation including hormonal studies of cancer patients and their families and a study of mechanisms of gene action at a biochemical level. This is a fine study which should be read by all workers dealing with the cancer problem.

IRA S. GOLDENBERG

THE BACTERIOLOGY OF TUBERCULOSIS. By Egons Darzins. Minneapolis, University of Minnesota Press, 1958. 488 pp. $10.00.

This book represents a very complete and comprehensive reference text for academic and clinical bacteriologists. Dr. Darzins has masterfully documented the important techniques used in the study of the tubercle bacillus and has integrated these descriptions with supporting experimental data and reviews of the literature. The book is divided into five sections in historical sequence which include morphology and cytology, sources of energy and growth, isolation and identification, types and pathogenicity, and experimental tuberculosis. In the preface of this book Dr. Darzins carefully describes his purposes. In part he writes, "In the course of the past twenty years many workers in the field of the bacteriology of tuberculosis have been published, dispersed in both well-known and less familiar

periodicals all over the world. Before further advance in tuberculosis research can be made, it is necessary to summarize the results already achieved; this is one of the aims of this book. Another of my objectives is to point out unsolved problems in the bacteriology of tuberculosis and to indicate recently developed experimental methods for the study of the tubercle bacilli."

For the young scientist embarking on tuberculosis research and without a vast background of experience, this book should be invaluable as a good summary of the field of experimental and diagnostic tuberculosis. The faculties of bacteriology departments in our colleges and universities should find this an excellent lecture and reference guide. Needless to say, I enthusiastically recommend this book for the library of all bacteriologists.

J. R. HENDERSON

THE BIOTIC WORLD AND MAN. By Lorus J. Milne and Margery J. Milne. Englewood Cliffs, N. J., Prentice-Hall, Inc., 1958. xiii, 530 pp. $7.50.

This elementary biology text for college undergraduates is intended to emphasize the importance of biology for man. Topics covered include the taxonomy, cytology, anatomy, physiology, biochemistry, embryology, genetics, ecology, and evolution of both plants and animals.

The discussions of physical and chemical processes do not require any prior knowledge of these subjects. Evolution is not specifically mentioned until relatively near the end of the book; the evidence for it is then marshalled from the variety of previously considered biological disciplines with the addition of appropriate paleontological data.

The Milnes indicate not only the economic value of organisms and of biological studies but also the aesthetic values. The latter are further emphasized by a large number of illustrations including some excellent photographs. As would be expected in a general text by only two authors, some minor errors have been made, but these are insignificant in respect to the volume as a whole.

Throughout the book natural history and ecology are considered in relatively greater detail than one is accustomed to finding in a beginning text. Perhaps the most unique feature is the final chapter in which the need for the intelligent use of natural resources and the problems of increasing human populations are considered.

The volume is recommended for consideration by teachers of basic biology.

G. A. CLARK, JR.

LABORATORY OUTLINE FOR GENERAL ZOOLOGY. 4th Ed. By George Edwin Potter. St. Louis, C. V. Mosby Company, 1958. 320 pp. $3.60.

Among the laboratory outlines available for use in introductory general zoology courses is this one by George Edwin Potter, now published in its fourth edition. The manual emphasizes morphology, with occasional attention to physiology (e.g. observations of gross behavior, experiments

on digestion, etc.). Sufficient material is provided for a year's course; changes in order are possible, as is selection of a smaller number of exercises for a shorter course. Representatives of the major phyla are considered; about a third of the manual is devoted to the vertebrates, with special attention to the frog. Included are exercises on cells and histology.

This publication, like most, is not perfect: one wonders at the value of providing diagrams outlined in gray to be traced over by the student; occasional specific instructions concerning matters of procedure (quizzes, recitation, etc.) would hardly apply to all courses. A more general question is suggested: is the emphasis on anatomy and neglect of physiology necessary or desirable? This question, of course, may be directed at most lab manuals and introductory zoology courses.

The author's stated aim is to provide sufficient guidance and practical direction for the student to progress on his own without being spoon-fed or feeling confused. This is a difficult balance to strike, but Potter does so with apparent success. Comprehensiveness makes flexibility possible. The student should find the suggested review outline and the questions on comparative aspects helpful if he gives them his attention.

Finally, in view of the current interest in improving science instruction at the secondary school level and providing stimulating material for capable students, high school teachers might well consider using manuals like this instead of the fill-in-the-blanks type. With wise selection of exercises and somewhat more supervision by the instructor, Potter's manual could be used below the college level.

MARIANNE DURAND

WARD 4, THE MALLINCKRODT RESEARCH WARD OF THE MASSACHUSETTS GENERAL HOSPITAL. By James Howard Means. Cambridge, Harvard University Press, 1958. 187 pp. $4.50.

This is the story, briefly and delightfully told, of the conception, growth, and flowering of a small clinical research unit, the Mallinckrodt Research Ward of the Massachusetts General Hospital. Dr. Means, the founder and long-time director (he prefers "guide") of Ward 4 as Jackson Professor of Clinical Medicine at Harvard Medical School, describes the impressive results of encouraging free exchange among physicians, "pure" scientists, and administrators in a congenial medical school-hospital environment.

The book is basically personality-centered. Dr. Means first pays tribute to the wisdom of the men like Edsall who recognized the need for full-time clinical investigators and provided them with support. Always stressing the virtues of "investigator-centered" research, the chapters that follow tell of the research teams that have utilized Ward 4, in spirit and substance, in their study of disease mechanisms. The investigators and their endeavors are most impressive: Aub and his studies on lead and calcium metabolism; Albright and the elucidation of parathyroid function and metabolic bone disease; Means and thyroid pharmacophysiology; Jones and his investigations of gastrointestinal function; Bauer and research on the nature of collagen diseases. Many of their pupils are mentioned, and,

always the wise physician, Dr. Means gives credit to the loyalty of the ward's benefactors and staff.

The style is informal and lucid. Apparently writing for both medical and nonmedical readers, the author boldly explains complex metabolic interrelationships for the benefit of all—with the aid of a glossary that would serve handsomely in any textbook of medicine.

To Dr. Means, Ward 4 symbolizes freedom of inquiry, scientific progress through the interchange of ideas, and the critical role of the patient in medical learning. His account of its first thirty-two years should provide inspiration and pleasure for all those interested in the making of modern medicine.

WILLIAM A. TISDALE

THE INCURABLE WOUND AND FURTHER NARRATIVES OF MEDICAL DETECTION. By Berton Roueché. Boston, Little, Brown, and Co., 1958. 177 pp. $3.50.

This is the second collection of narratives to be presented in book form by Mr. Roueché. As was the case with his first book, *Eleven Blue Men*, each of these narratives has appeared first in *The New Yorker* magazine. The contents of this volume include six narratives which concern themselves respectively with the following subjects: amnesia; the direct transmission of rabies to man by insectivorous bats found in this country; a case of carbontetrachloride poisoning; the history of aspirin—its role as an analgesic and antipyretic and its potential as a poison; the operations of the Poison Control Center in New York City's Department of Health; and the case history of a patient with periarteritis nodosa who exhibits a clinical picture consistent with manic-depressive psychosis while receiving large daily doses of cortisone.

Each of these narratives gives adequate demonstration of the author's thorough study and comprehension of the medical subject matter at hand. This combined with his talent as a story-teller results in exciting reading for the lay and professional person alike. Whereas Sir Arthur Conan Doyle brought the skill and techniques of the diagnostician to detective fiction, Mr. Roueché has enhanced these narrations of medical topics with his skill as a writer of mysteries. In summary, this volume offers light, informative, intelligent, and enjoyable relaxation for the clinician or academician who is not a regular reader of *The New Yorker*.

WILLIAM L. KISSICK

ADDITIONAL BOOKS RECEIVED

Our Nuclear Adventure; Its Possibilities and Perils. By D. G. Arnott. New York, Philosophical Library, 1958. 170 pp. $6.00.

The Mind of the Murderer. By W. Lindesay Neustatter. New York, Philosophical Library, 1957. 224 pp. $6.00.

Safety Techniques for Radioactive Tracers. By J. C. Boursnell. New York, Cambridge University Press, 1958. 67 pp. $1.75.

Morphological Integration. By Everett C. Olson and Robert L. Miller. Chicago University of Chicago Press. 317 pp. $10.00.

A Visit to the Hospital. By Francine Chase. New York, Grosset & Dunlap, 1957. 68 pp. $1.50.

Morphology and the Evolution of Man. By J. J. Livingston. New York, Vantage Press, 1957. 133 pp. $3.00.

Communication, Organization, and Science. By Jerome Rothstein. Indian Hills, Colorado, The Falcon's Wing Press, 1958. 110 pp. $3.50.

The Atomic Age and Our Biological Future. By H. V. Bronsted. New York, Philosophical Library, 1957. 80 pp. $2.75.

Topics in Microbial Chemistry. By F. M. Strong. New York, J. Wiley & Sons, Inc., 1958. 166 pp. $5.00.

Ciba Foundation Colloquia on Ageing. Vol. 3. *Methodology of the Study of Ageing.* Editors, G.E.W. Wolstenholme and Cecilia M. O'Connor. Boston, Little, Brown and Co., 1957. 202 pp. $6.50.

Animal Behavior. By John Paul Scott. Chicago, University of Chicago Press, 1958. 281 pp. $5.00.

The Preservation of Youth. By Moses Ben Maimon (Maimonides). New York, Philosophical Library, 1958. 92 pp. $2.75.

Comparative Physiology of the Nervous Control of Muscular Contraction. By Graham Hoyle. Cambridge, At the University Press, 1957. 147 pp. $3.00. (Cambridge monographs in Experimental Biology, No. 8)

Television in Science and Industry. By V. K. Zworykin, E. G. Ramberg, and L. E. Flory. New York, J. Wiley & Sons, 1958. 300 pp. $10.00.

The Population Ahead. By Roy G. Francis. Minneapolis, University of Minnesota Press, 1958. 160 pp. $3.75.

The Only Baby. Poems and Notes on Psychiatric Theory. By Sheldon Cholst. New York, Whittier Books, Inc., 1958. 72 pp. $2.50.

Fat Consumption and Coronary Disease: The Evolutionary Answer to this Problem. By T. L. Cleave. New York, Philosophical Library, 1958. 40 pp. $2.50.

Cancer and the Atomic Age. By Clement A. Tavares. New York, Vantage Press, 1958. 198 pp. $3.50.

Trends in Gerontology. By Nathan W. Shock. 2d ed. Stanford, Calif., Stanford University Press, 1957. 214 pp. $4.50.

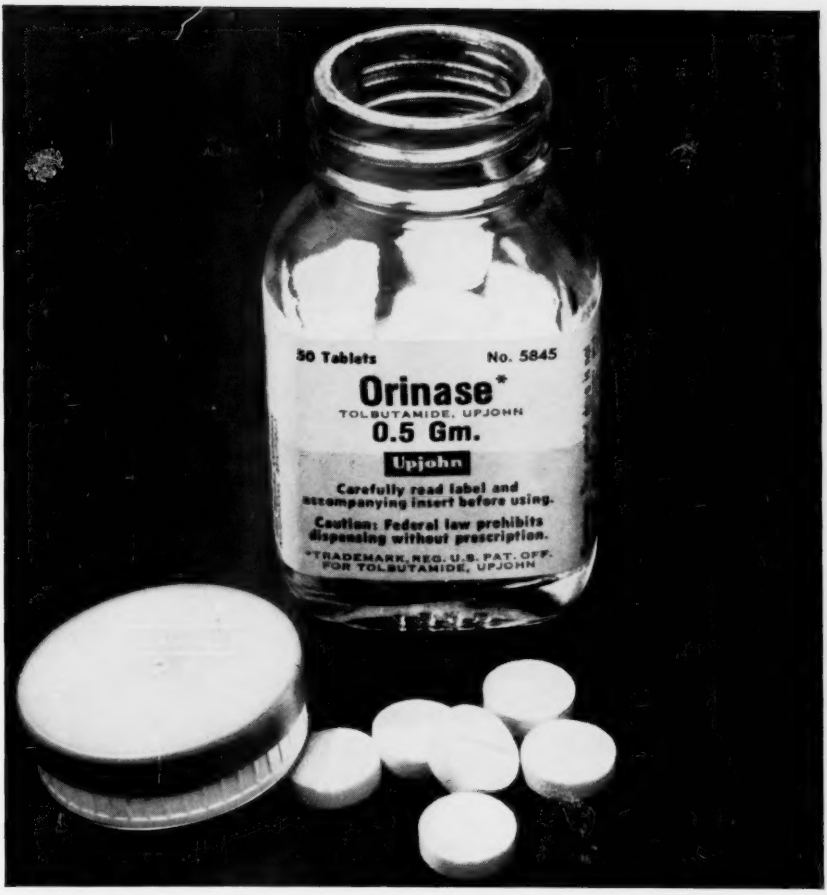
On the Early Development of Mind. By Edward Glover. New York, International University Press. 440 pp. $7.50.

Anatomical Atlas. By Maud Jepson. New York, Rinehart & Co., 1958. 29 pp. $0.95.

Home Conditions: A Sociomedical Study of 1066 Hospitalized Patients With Skin and Venereal Diseases. By Esbern Lomholt. Copenhagen, Rosenkilde and Bagger, 1958. 100 pp.

Physico-Chemical and Immunological Studies on the Virus of Foot-and-Mouth Disease and its Host Tissue Microsomes. By Axel Randrup. Copenhagen, Ejnar Munksgaard, 1957. 68 pp.

The Fetal Pig, A Photographic Study. Revised ed. By W. L. Evans and Addison E. Lee. New York, Rinehart & Co., 1958. 44 pp. $1.25.



Orinase: a year of experience

A review of the first year of general use of Orinase* shows that the infant drug of June, 1957, had become an accepted and trusted therapeutic tool by June, 1958.

Because Orinase was used clinically in more than 18,000 patients prior to its release to the medical profession, Upjohn was confident of how well it would perform. The physician, naturally, was cautious in his dealings with this revolutionary new agent for diabetes control; he moved slowly. But, as the months passed, Orinase gained the confidence of physicians and patients, and, by the end of the first year of general use, more than 250,000 diabetics were being controlled on oral therapy.

It has recently been conclusively demonstrated that Orinase, in the presence of a functional pancreas, effects the production and utilization of *native* insulin via *normal* channels. Now that the mode of action is established, additional hundreds of thousands of diabetics should soon be enjoying a more normal life, thanks to a more logical therapy.

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